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Antibiotics 1955: A Discussion of Recent Developments, Use, and Side Effects — *Henry Welch*

Carbomycin — *Wallace E. Herrell*

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VOL. 168 NO. 7 • WHOLE NUMBER 2869 • JULY 1955

INTERNATIONAL RECORD OF MEDICINE

Antibiotics 1955: A Discussion of Recent Developments, Use, and Side Effects 449
Henry Welch

Carbomycin 463
Wallace E. Herrell

EDITORIAL SURVEY

Health Through Travel 473

Pictorial Highlights of the First International Symposium on Health and Travel 476

The First International Symposium on Health and Travel

Part I*

The Physician as Traveler: Introduction to the First International Symposium on Health and Travel 480
Félix Martí-Ibáñez

When Children Travel 486
I. Newton Kugelmass

When People Who Are Not Young Travel 496
William T. Foley

Infections and Travel 500
Elmer H. Loughlin

GENERAL PRACTICE CLINICS

Advance Reports from Current Medical Meetings

The New Steroids and Things to Come 506
Joseph J. Bunim

The Clinical Use of Erythromycin 507
Saul Solomon

Antibiotics in Childhood 507
Harry Shwachman

Needle Biopsy of the Kidney 509
Maxwell Wintrobe

The Nephrotic Syndrome in Children 509
Donald Gribetz

The Value of an Optimal Effective Dose of Anticholinergic Drugs in the Treatment of Peptic Ulcer 510
David C. H. Sun and Harry Shay

The Effect of Antibiotics on Intestinal Absorption of Vitamin B_{12} in Disorders of the Gastrointestinal Tract 511
James A. Halsted, Marian E. Swendseid, Marvin Gassler, and Peter M. Lewis

Iatrogenic Aspects of Cardiovascular Disease 511
Perrin H. Long

Fortified Broad-Spectrum Antibiotics as an Adjunct in Surgical Treatment of the Young and the Aged and Debilitated Patient 512
Aaron Prigot

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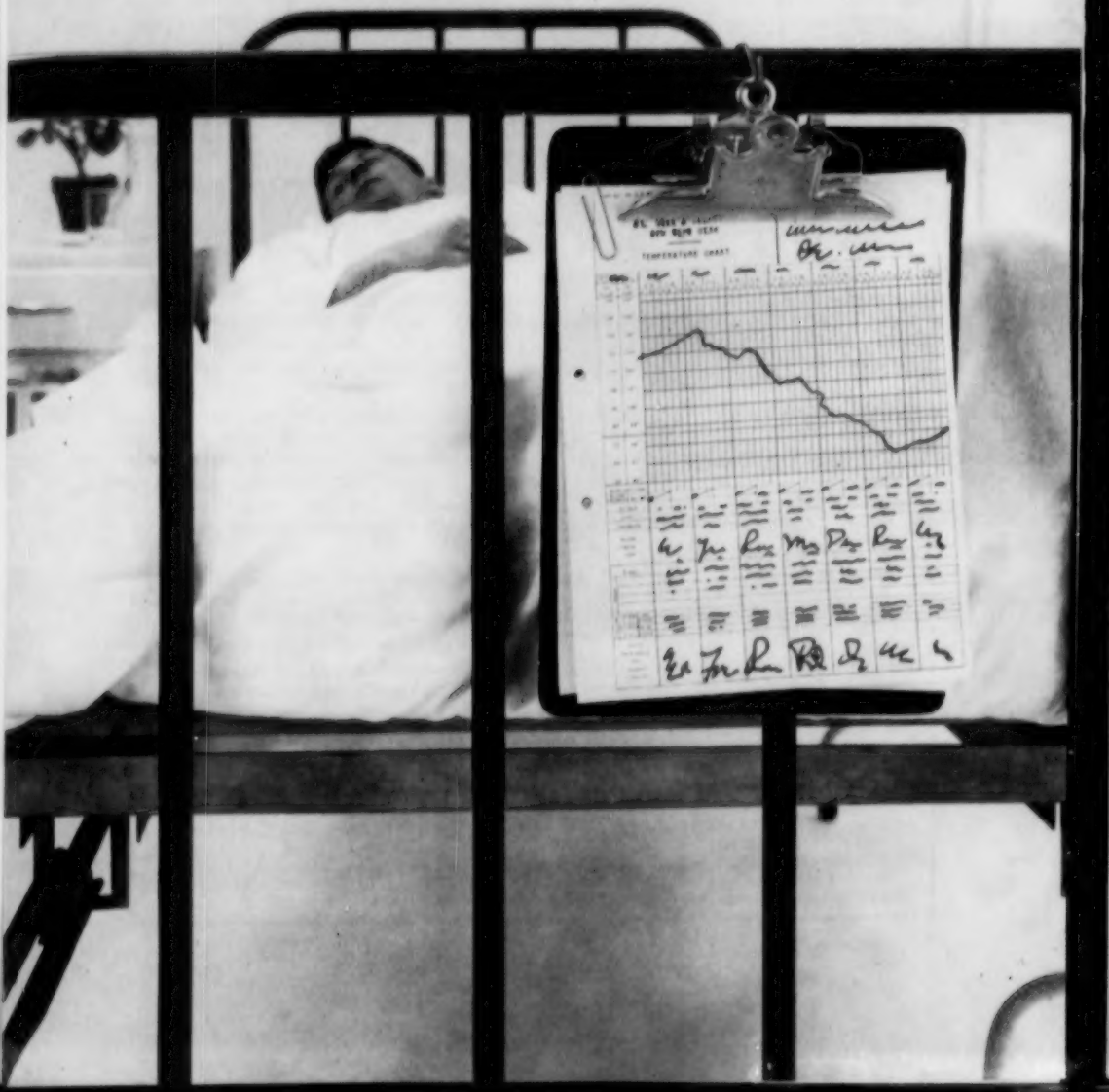

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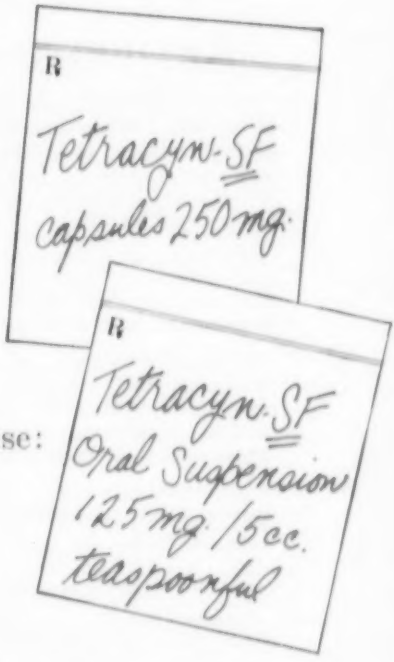

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1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952. 2. Marti-Ibáñez, F.: Antibiotic Med. *1*:247 (May) 1955. 3. Dumas, K. J.; Carlozzi, M., and Wright, W. A.: Antibiotic Med. *1*:296 (May) 1955. 4. Milberg, M. B., and Michael, M., Jr.: Ann. New York Acad. Sc., In press. 5. Prigot, A.: Ibid.

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1954—1955

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Henry Welch

DIVISION OF ANTIBIOTICS, FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C.

The antibiotics industry as such was initiated in a very small way early in 1943. Through government cooperation a program was established by the War Production Board, the Army, the Navy, the National Research Council, and the Food and Drug Administration for the manufacture of commercial penicillin. The War Production Board made it possible to get scarce material for construction of plants. Through the National Research Council a careful clinical program for determining safety and efficacy of the drug was made possible, and the Army, the Navy, and the Food and Drug Administration set up standards of procurement for the drug, since at that time the Armed Forces were to receive all of the drug made in this country.

Under an agreement between the Army and the Food and Drug Administration each batch of penicillin produced was checked prior to shipment overseas. The drug was very crude, having a potency of approximately 200 units/mg. It was noncrystalline, dark brown in color, and quite painful on injection. The great bulk of the drug was produced by the bottle method and only small amounts were made available. By the end of 1944 there were 20 plants producing penicillin, the great bulk by bottle fermentation, where milk bottles and whiskey bottles, etc., were used, while a few plants were producing the drug by deep-tank fermentation. It was early recognized that if we were to obtain any large amount of penicillin it would have to be by deep-tank fermentation. In the early days it was visualized that tanks as large as 5,000 gallons would be necessary. Most of the industry and Government officials felt that the needs for the Army and the civilian population, when it was released to them, would never exceed 5,000 Kg. a month. Today 30,000 gallon tanks are used and production requirements exceed the 5,000 Kg. estimate many times.

Lecture presented before The Morrisania City Hospital Alumni and Clinical Society on April 18, 1955.

Penicillin became available for the civilian population in 1945 and by that time the purity of the drug had been improved considerably so that the calcium salt, which was the one used to the greatest extent, had a potency on the order of 1,200 units/mg. The crystalline drug, which soon appeared, had a potency of 1,667 units/mg. All during the war years and for some time thereafter 20 manufacturers in this country produced practically the entire world's supply of penicillin. Competition as such did not exist. All that was produced was consumed and the price was high. The Army paid as much as $20 for each 100,000 units. By contrast, during the past winter the Army purchased penicillin in vials packed for shipment overseas in wooden cases for five cents for each 300,000 units; in other words, less than two cents per 100,000 units. In contrast to the early days, competition is extremely keen now and instead of 20 manufacturers of penicillin today we have only 10. As a matter of fact, the great bulk of penicillin is produced by 4 of these 10 who account for some 70 per cent of the production.

Production of penicillin in this country started an industry that had no capital assets in 1942 but today has a capital worth of about one billion dollars. In less than 15 years a number of other antibiotic drugs have found their way into the therapy of infectious diseases. In table I are shown the 18 useful antibiotics of the 3,000 to 4,000 that have been described in the literature.

In addition to these there are hundreds of other antibiotics awaiting tests on the shelves of those manufacturers still in the antibiotics field. In addition to the 10 manufacturers of penicillin, there are three others producing antibiotics, and these 13 account for the great bulk of the world's supply of antibiotics. It will be noted from table I that, for all practical purposes, about one antibiotic of importance or usefulness has appeared for each year, the most recent of these being nystatin, anisomycin, and cycloserine. As a matter of fact, cycloserine is still not available for distribution but is under test, primarily for its usefulness in the treatment of tuberculosis.

TABLE I

Useful Antibiotics of the 3,000 to 4,000 That Have Been Described

Antibiotic	Year	Antibiotic	Year
Penicillin	1929–1943	Fumagillin	1950
Tyrothricin	1939	Oxytetracycline	1950
Streptomycin	1943	Viomycin	1950
Bacitracin	1945	Nystatin*	1951
Chloramphenicol	1947	Erythromycin	1952
Polymyxin	1947	Carbomycin	1952
Dihydrostreptomycin	1948	Tetracycline	1953
Chlortetracycline	1948	Anisomycin*	1954
Neomycin	1949	Cycloserine*	1955

* These antibiotics have become available recently or are still under study.

TABLE II

Antibiotic Production for the Past 11 Years

Year	Antibiotic	Pounds	Approximate value, dollars
1943	Penicillin	29	3,000,000
1944	Penicillin	3,200	
1945	Penicillin	14,000	
1951	Penicillin	636,000	137,000,000
1953	Penicillin	756,000	58,000,000
1954	Penicillin	860,000	63,000,000
1946	Streptomycin	3,800	11,400,000
1953	Streptomycin and dihydrostreptomycin	375,200	35,000,000
1954	Streptomycin and dihydrostreptomycin	494,000	40,000,000
1953	Broad-spectrum*	417,600	137,000,000
1954	Broad-spectrum*	440,000	150,000,000
1954	Feed supplements	490,000	19,000,000
1954	All antibiotics (est.)	2,284,000	272,000,000

* The broad-spectrum antibiotics are chlortetracycline, oxytetracycline, tetracycline, and chloramphenicol.

In table II the changes in production and approximate value of antibiotics listed up through 1954 are shown. You will note that only 29 pounds of crude penicillin were produced in 1943 and that this amount had a value at the manufacturers' level of about $3,000,000. Production increased more than 100 times in 1944 to 3,200 pounds. In 1945 we exceeded by a considerable amount the original estimate of 5,000 Kg., which was expected to be sufficient to supply the world demand. In 1945, 14,000 pounds, or more than 6,000 Kg., were produced. Six years later, in 1951, penicillin was being produced at the rate of 636,000 pounds a year, with a value of $137,000,000. Competition in the industry became extremely keen from 1951 on, and although 756,000 pounds were produced in 1953 the value was less than half that of the 636,000 pounds produced in 1951.

The history of the production of streptomycin is not markedly different, but because of the experience in production methods obtained with penicillin, we produced in 1946, the first year that streptomycin became available commercially, some 3,800 pounds. This drug too on its first use was expensive, in the neighborhood of $15 per Gm., and thus the 3,800 pounds had a value of more than $11,000,000. In spite of this the competition in penicillin was reflected in the price of streptomycin by 1953, and although 375,000 pounds were produced (100 times as much as was produced in 1946) the value increased only 3 times. Thus, 3,800 pounds were worth $11,000,000 in 1946 and 375,000 pounds were worth only $35,000,000 in 1953. There is a contrast in the price picture presented by the broad-spectrum drugs. These four

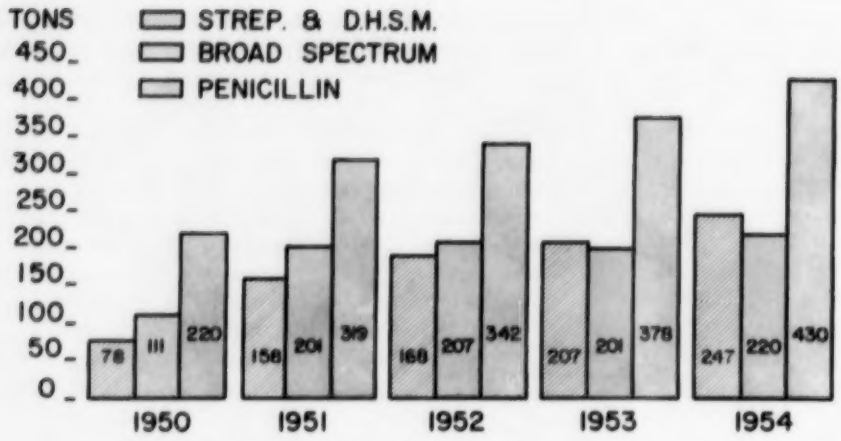

FIG. 1. Yearly production for antibiotics.

drugs have maintained their price pattern reasonably well since their discovery and commercial availability. In 1953 more than 417,000 pounds of these drugs were produced with an approximate value of $137,000,000. In 1953, 440,000 pounds valued at $150,000,000 were made available.

The broad-spectrum antibiotics and penicillin have further uses other than the prophylaxis and treatment of disease, and a goodly amount is used in the promotion of animal growth. Some 490,000 pounds were produced in 1954 for feed supplements. It will be noted from the figure that the total for all antibiotics in 1954 was some 2,284,000 pounds, with an approximate value of more than $272,000,000.

In spite of the fact that there are 17 antibiotics available for use in this country, streptomycin, dihydrostreptomycin, the broad-spectrum antibiotics, and penicillin are the ones that are used to the greatest extent. In figure 1 the change in production during the past five years is shown. Streptomycin and dihydrostreptomycin, which were produced at the rate of about 78 tons a year in 1950 had increased to nearly 250 tons in 1954. The broad-spectrum antibiotics produced in 1950 at the rate of 111 tons had increased to 220 tons by 1954. Penicillin is still by far the most useful drug, since it was produced in 1950 at the rate of 220 tons and had increased in 1954 to 430 tons.

There are a large number of antibiotic preparations now available to the physician in this country. For those antibiotic preparations sold in greatest quantity there are more than 300 products available for clinical use. The greatest number of preparations, 150, available contain penicillin. There are 38 streptomycin and dihydrostreptomycin preparations, 47 chlortetracycline and tetracycline preparations, 25 oxytetracycline preparations, 15 chloramphenicol preparations, and 27 bacitracin preparations.

The rapid absorption and excretion of the soluble salts of penicillin has resulted in the development of a number of so-called "insoluble" salts in order to obtain

more prolonged blood concentrations. The first of these was procaine penicillin, which at the present time constitutes the great bulk of the penicillin sold in the United States. In figure 2 the blood concentrations obtained following various preparations of penicillin are given. It will be noted that crystalline potassium penicillin in the majority of patients shows a peak concentration of 3 units/ml. and will maintain blood concentrations for about nine hours following an intramuscular injection of 300,000 units. With procaine penicillin in aqueous suspension concentrations obtained are as high as 1.5 unit/ml., but these are prolonged for as long as 24 hours. Benzylamine penicillin, a less soluble salt than procaine, maintains blood concentrations for about 48 hours in the majority of patients and has a peak concentration of 0.6 unit /ml. When aluminum monostearate is added to procaine penicillin in oil, the blood concentration is prolonged for about three days in the majority of patients, with a peak concentration of approximately 0.5 unit /ml. This drug has been used probably more than any other in the treatment of syphilis. The penicillin preparation that prolongs blood concentrations to the greatest extent is dibenzylethylenediamine dipenicillin G; with 300,000 units injected intramuscularly, peak blood concentrations in the majority of patients of about 0.26 units /ml. are obtained and the drug is demonstrable in the blood for as long as seven days. A single injection of 1.2 million units of this drug will give continuous blood concentrations for approximately one month. The drug is highly insoluble in body fluids (about 200 units /ml.) and has found extensive usefulness in the prophylaxis of streptococcal infections in patients with a history of rheumatic fever.

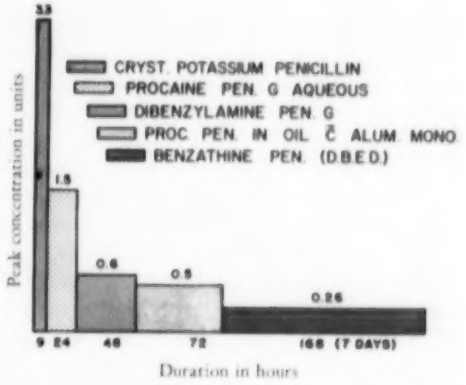

FIG. 2. Peak concentration and duration of penicillemia following intramuscular injection of five preparations (300,000 units/ml.).

Although both streptomycin and dihydrostreptomycin are used in combination with other drugs for the treatment of a variety of infections, the greatest single use of these drugs is in the treatment of tuberculosis. The doses that are most commonly used are 1 Gm. daily or 1 Gm. twice weekly intramuscularly, combined with either isoniazid or *p*-aminosalicylic acid. In figure 3 the blood concentrations obtained with single doses of streptomycin of from 0.25 Gm. to 1 Gm. are shown. It will be noted with the commonly used dose, namely, 1 Gm., that blood concentrations

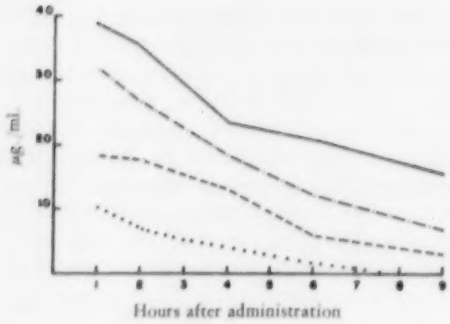

FIG. 3. Blood serum concentrations of streptomycin following intramuscular administration. ——— 1.0 Gm.; — — — 0.75 Gm.; — · — 0.5 Gm.; · · · · 0.25 Gm.

approaching 40 μg. are obtained within an hour of injection. Concentrations of streptomycin in excess of that usually necessary to inhibit the activity of the tubercle bacillus are maintained for at least nine hours. As a matter of fact, measurable blood concentrations of this drug can be observed for at least 24 hours after the injection of 1 Gm. It will be noted that there is a relationship between the amount of the drug and the concentration of streptomycin found.

The broad-spectrum drugs are administered orally in the great majority of cases in divided doses of 1 to 2 Gm. daily. In figure 4 blood concentrations obtained following oral administration of the four broad-spectrum drugs are shown.

In this figure all patients were given 0.5 Gm. every six hours or 2 Gm. daily. It will be noted that the highest blood concentrations obtained are with chloramphenicol and that these vary from 4 to 6 μg./ml. of serum. The concentrations of the three tetracyclines vary from 1 to 2 or 3 μg./ml., tetracycline giving somewhat higher concentrations than the other two analogues. Although the differences in blood concentrations obtained between chlortetracycline and oxytetracycline are not great, in our experience oxytetracycline tends to give somewhat higher concentrations than its analogue, chlortetracycline.

The tetracycline antibiotics have been used to a great extent during the past two years. Because of the close chemical relationship, there has been a tendency to sub-

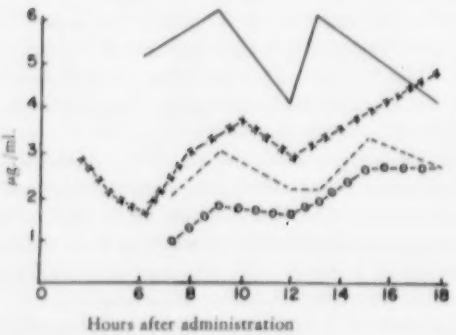

FIG. 4. Average serum concentration of four broad-spectrum antibiotics (0.5 Gm. orally every six hours). ——— Chloramphenicol; — — — oxytetracycline; o———o chlortetracycline; and x———x tetracycline.

TABLE III

Variations in the Antimicrobial Activity of the Tetracyclines

Genus	No. strains	Level activity, μg./ml.*	Strains sensitive to, %		
			Chlortetracycline	Oxytetracycline	Tetracycline
Staphylococci	338	0.78	63.6	8.8	63.0
Aerobacter	89	0.78	38.2	28.1	59.5
Escherichia	118	0.78	22.0	16.1	71.1
Salmonella	51	0.78	13.7	1.9	64.7
Shigella	48	0.78	25.0	14.6	64.6
Str. viridans	39	0.312	51.2	25.6	41.0
Diplococci	30	0.078	76.6	56.6	73.3
Str. pyogenes	49	0.078	30.6	8.1	24.4
Str. faecalis	11	0.312	81.0	0.0	54.5

* Antibiotic level at which the greatest difference in activity occurs.

stitute one for the other in the treatment of a variety of infections. However, there is evidence that these drugs do have differences in their antimicrobial activity. It is known, for example, that oxytetracycline is active in tuberculosis and chlortetracycline is not. It has been shown that oxytetracycline is superior to its analogues in the treatment of amebiasis. On the other hand, chlortetracycline is more active against certain of the staphylococci than are its two analogues. We have tested several hundred strains of microorganisms to determine the difference of activity of these drugs and the data obtained are shown in table III. It will be noted that insofar as the staphylococci are concerned chlortetracycline and tetracycline are the most active of the three tetracyclines against the 338 strains tested. At a level of 0.78 μg./ml., 63 per cent of the strains are sensitive to chlortetracycline and tetracycline, whereas approximately 9 per cent are sensitive to oxytetracycline. With the *Aerobacter*, 59 per cent of 89 strains tested were sensitive to tetracycline at the 0.78 μg./ml. level, while 28 and 38 per cent were sensitive at this level to oxytetracycline and chlortetracycline, respectively. With *Escherichia* a similar situation prevails, since 71 per cent of 118 strains are sensitive to tetracycline and only from 16 to 22 per cent are sensitive to the other two drugs. This same situation obtains with the *Salmonella* and *Shigella*. With the *Str. viridans* and diplococci (pneumococci) we find chlortetracycline the most active and this prevails with *Streptococcus pyogenes* and *Streptococcus faecalis*. In a general way it would appear that insofar as the gram-positive organisms are concerned chlortetracycline appears to be the most active of the three, while with the gram-negative group tetracycline is the most active. It should be noted that among the several hundred strains tested, on occasion with specific strains, oxytetracycline was by far the most active of the three, further emphasizing the need for careful sensitivity studies, particularly in those chronic infections requiring prolonged treatment, such as subacute bacterial endocarditis and osteomyelitis.

The wide use of antibiotic drugs during the past 10 to 15 years has brought with it many problems from the standpoint of side reactions that all drugs are prone to cause. One of the outstanding problems that we have had has been the blood dyscrasias following use of chloramphenicol. There seems to be no doubt that under certain circumstances chloramphenicol can cause serious blood dyscrasias. This propensity for chloramphenicol to cause blood dyscrasias has been attributed to the nitrobenzene portion of its molecular structure. There seems to be little doubt that this type of structure in a molecule lends itself, for some reason now unknown, to the development of changes in the blood of those individuals treated with the drug. The relatively few blood dyscrasias that occur following the use of chloramphenicol, however, would indicate that if the nitrobenzene radical is responsible, its responsibility does not rest with an inherent toxicity of that portion of the molecule, but it seems more likely that the blood dyscrasia is initiated through a sensitization phenomenon and an ability of the molecule to form partial antigens with the body proteins of some individuals. From a two year survey that has been made in the United States, it is obvious that blood dyscrasias occur in females more frequently than males—about three to one—and, furthermore, that the great majority of patients are children of 10 years or younger. In the survey just referred to we reviewed a total of 1,987 case histories. Our interest was not only in the blood dyscrasias following administration of chloramphenicol but those following other drugs as well. From table IV it will be noted that there are 84 cases in which chloramphenicol was the only drug administered; 68 of these resulted in aplastic anemia. The second category utilized was for those patients who had been administered chloramphenicol and other drugs as well, and it was therefore impossible to scientifically determine which drug was responsible. In this category there were 230 cases of which 148 were aplastic anemia.

Of considerable interest are those patients in whom chloramphenicol was not used. It will be noted that there were 1,446 blood dyscrasias in this group, including 403 cases of aplastic anemia. There are innumerable drugs and exposure to chemicals involved in these cases including barbiturates, sulfonamides, insecticides, various chemicals, and antibiotics. As a matter of fact, the drugs administered include most of those listed in the Pharmacopoeia. Two hundred and twenty-seven cases

TABLE IV

Two Year Survey of Blood Dyscrasias Following Drug Administration

Antibiotic	No. cases	No. aplastic anemia
Chloramphenicol only	84	68
Chloramphenicol and other drugs	230	148
Chloramphenicol not used	1,446	403
Cases eliminated	227	
Total	1,987	619

TABLE V

1953 Survey of Anaphylactoid Reactions

Antibiotic	No. reactions	No. fatal
Procaine penicillin	55	18
Penethamate (neo-penil)	26	5
Penicillin O	2	0
Benzathine (tablet)	1	1
Streptomycin	4	1*
Broad-spectrum antibiotic	0	0
Total	88	25

* Intrathecal.

were eliminated for insufficient evidence of a blood dyscrasia or not enough evidence to determine the category in which to place the case. After the first wide publicity given to the problem of blood dyscrasias following the administration of chloramphenicol, the drug went into almost complete disuse for several months. In the labeling of the drug, clinicians were warned not to use the drug in minor infections and to follow the patient carefully after the drug was administered. In a general way, I should say that the drug has gradually come back to its proper place in the physician's daily practice and, although only half as much of the drug is being used now as was used in its early days, it is used with considerably more discretion.

The wide use of penicillin has also caused its difficulties. There have been an increasing number of reports concerning sensitization to the various penicillin salts and preparations. Because of this we made a survey in 1953 to determine the incidence of anaphylactoid reactions that had occurred following administration of penicillin and other antibiotics. In table V the results of this survey are shown. It will be noted that with procaine penicillin, which is the penicillin salt of greatest use in this country, there were 55 anaphylactoid reactions, 18 of which were fatal. In practically all instances patients who had a fatal outcome died within five minutes of the administration of the drug. There were 26 reactions from penethamate, the diethylaminoethyl ester penicillin hydriodide, and 5 of these were fatal. From penicillin O, which is a salt developed primarily for use in those patients sensitive to penicillin G, there were 2 reactions, neither of which was fatal. There was 1 reaction and 1 fatality from oral penicillin, a tablet containing benzathine penicillin. Four cases of the anaphylactoid type resulted from the administration of streptomycin, 3 cases from intramuscular injection and 1 from intrathecal. The 1 fatality followed intrathecal administration. We found no anaphylactic-like reactions following the use of the broad-spectrum antibiotics. Thus the 1953 survey, which covered small sections of the country (actually 10 of the large cities and the surrounding areas) revealed 88 anaphylactoid reactions with 25 fatalities. On the basis of these data and the quantities of penicillin utilized, we estimate that we have in this country some 200 or more anaphylactoid reactions yearly, with a fatality rate of between 30 and 40 per cent.

TABLE VI

Penicillin in Market Milk (1955)

District	Samples		Concentration* u/ml. (av.)
	Tested	Positive	
Atlanta	26	1	.006
Baltimore	26	5	.01
Boston	31	4	.014
Buffalo	33	5	.007
Chicago	31	2	.018
Cincinnati	25	3	.008
Denver	44	4	.007
Kansas City	26	1	.006
Los Angeles	27	6	.03
Minneapolis	40	0	0
New Orleans	26	2	.011
New York	25	5	.016
Philadelphia	26	6	.021
San Francisco	36	5	.021
Seattle	25	6	.015
St. Louis	27	0	0
Total	474	55 (11.6%)	

* Minimum, .003 u./ml.; maximum, .08 u./ml.

The extension of the uses of antibiotics to fields other than prophylaxis and therapy of human disease has magnified our problems from the standpoint of side reactions and possible public health significance. Antibiotics are used in animal nutrition, for promotion of growth in swine, chicks, and poults. Therapeutic and prophylactic use of antibiotics is made in animals, such as cows, beef cattle, swine, chicks, and mink. These drugs are now being used as crop sprays to prevent blight in apple, pear, walnut, and beans, and bacterial disease of tobacco, tomatoes, peppers, cherries, and others. There now are before us proposals for their use as food preservatives, and studies have already been made to show the value of antibiotics in the preservation of vegetables, fish, beef, chickens, and other perishables.

A tremendous market, particularly for penicillin and the broad-spectrum drugs, has developed in the past few years in the field of veterinary medicine. Because of the incidence of mastitis in cattle in this country, large quantities of the drugs are used in the treatment of this infection. From our own studies in cows, we know that intramammary infusion of the antibiotics is followed by elimination of the antibiotic in the milk from one day to several weeks, depending on the type of preparation. Although the farmer is warned to discard milk from treated cows for a period of at least three days following medication, we are quite sure that this is not done. If the cow with mastitis is cleared of infection from a physical standpoint in a matter of 24 to 48 hours, the cow is immediately put back on the milking line. As a result of this, antibiotics do get into the milk supply. During the past two years

we have made two surveys of market milk to determine the incidence of positive samples and the concentration of antibiotic in the milk. Our first survey in 1954 showed a very low incidence, something on the order of 3 per cent, and extremely small quantities of drug. In 1955 a second survey was completed, which was considerably more extensive and the results are shown in table VI.

It should be pointed out that the great majority of milk samples containing antibiotics contained penicillin. In all of the samples studied in both surveys we found only one or two showing evidence of other antibiotics. In the table it will be noted that we examined some 474 samples from 16 different areas in the country and found 55 positive samples or 11.6 per cent. All samples in this group contained penicillin, proved by inactivation with penicillinase. The average concentrations are given in the table. There were only two areas in which no antibiotic could be demonstrated, namely, Minneapolis and St. Louis. We found a minimum of 0.003 unit /ml. and a maximum of 0.08 unit /ml. Thus, if a person drank a liter of milk a day, he would consume some 80 units of penicillin. We have not come to a conclusion as to the public health significance of concentrations of antibiotics in the milk supply. Obviously there is a possibility of the emergence of resistant strains of organisms; there is the question of whether or not these amounts would affect the oral or intestinal flora; but perhaps the most important question to be solved is whether or not these amounts of antibiotics would sensitize the nonsensitive individual on prolonged use or cause a reaction in the exquisitely sensitive individual.

In table I you will remember that the drug cycloserine was listed. This is the newest of the antibiotics isolated and under test for its clinical usefulness. In February of this year the first reports of the effectiveness of this drug were made at the Atlanta meetings of the Veterans Administration—Army—Navy Chemotherapy Conference

TABLE VII

In Vitro Inhibition of Various Strains of Bacteria by Cycloserine

Organism	No. strains	Minimum inhibitory concentration of cycloserine, μg./ml.
E. coli	10	100–125
Shigella	10	50–100
Aerobacter	10	100–500
Klebsiella	10	25–500
Salmonella	10	50–100
Pseudomonas	10	100–1000
Proteus	10	125–500
Beta hemolytic streptococci	10	50–250
Enterococci	10	50–250
Str. viridans gp.	2	125
M. pyogenes (aureus)	9	50–100
B. circulans	2	1000
D. pneumoniae	7	6.25–125
C. diphtheriae	2	<62.5
M. phlei	5	<62.5–125

on Tuberculosis.[1, 2] Cycloserine is an interesting drug in that its in vitro activity is apparently quite low although it appears to be reasonably active in vivo. In table VII the in vitro inhibition concentrations of cycloserine against a number of strains of bacteria are given. It will be noted that for all practical purposes, when compared with other available antibiotics, it is not a very highly antibacterial drug. We have evidence, however, that in certain types of resistant chronic urinary type infections the drug has been shown to be quite effective, in many instances where other antibiotic treatment failed. I should point out that although early studies indicated the same kind of activity for the tubercle bacillus, namely on the order of 30 to 50 μg., Cummings of the Veterans Administration has shown that the drug is active against human virulent tubercle bacilli in concentrations of from 2 to 5 μg./ml.[3] In a general way the drug is more active against the tubercle bacillus than any of the other genera tested. Preliminary studies indicate that the drug may be acting against the tubercle bacillus by actual lysis of the organism. From our own studies it appears that the opsonocytophagic activity of the blood serum against staphylococci and other organisms is increased following administration of cycloserine. Of the 117 strains we have tested, the average activity of the drug is 62 μg./ml.

In figure 5 the structure of cycloserine is shown. I have placed in this figure the structure of serine as well, so as to show the relationship of the two drugs. It will be of interest that in the April issue of ANTIBIOTICS AND CHEMOTHERAPY there appeared a paper describing oxamycin and including the structure of the drug.[4–7] These two drugs, oxamycin and cycloserine, are identical. It may be of interest to you too that a third company has also isolated this drug,[8] and that all three had set the drug aside some time ago as having too low activity for its toxicity to be a useful chemotherapeutic agent.

In figure 6 the blood serum concentrations that are obtained with cycloserine following various doses are shown. With the dose now being used, namely, 1 Gm. daily, it will be noted that following divided oral doses of 0.25 Gm. each, concentrations as high as about 20 μg./ml. are obtained. We carried out these studies for several days and the blood concentrations seem to plateau between 20 to 30 μg./ml. following continuous oral administration of 0.25 Gm. every six hours. A similar phenomenon occurs with the higher doses, beginning with the third to fourth day. It should be noted that the drug produces somewhat higher blood concentrations than other antibiotics on the same dosage regimen. At the present time in studies being conducted on tuberculosis the dose used is 500 mg. twice daily.

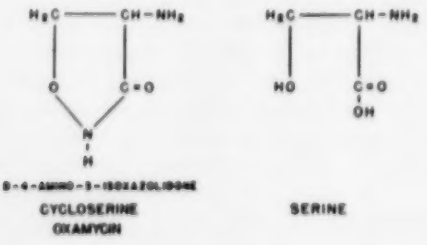

FIGURE 5

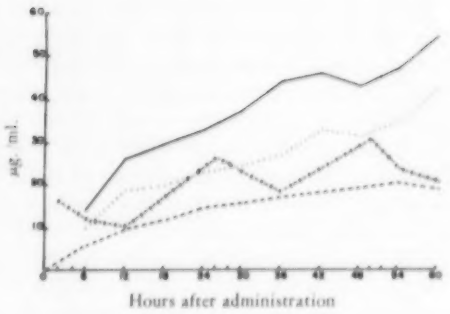

FIG. 6. Blood serum concentrations of cycloserine following divided oral doses. ——— 750 mg. every six hours; · · · · 500 mg. every six hours; – – – 250 mg. every six hours; and x–x–x–x 500 mg. every 12 hours.

In figure 7 the various concentrations obtained in urine following the same doses, namely 1, 2, and 3 Gm. daily in divided doses, are shown. The drug is excreted rapidly and in probably higher concentrations than the broad-spectrum drugs following oral administration. Very high concentrations of the drug are shown in the urine shortly after the first dose and with 750 mg. every six hours concentrations close to 1,200 μg. /ml. may be obtained. A concentration of 450 μg. /ml. is obtained with a dose of 1 Gm. daily, when 250 mg. is given every six hours.

Cycloserine is an interesting drug from the standpoint of the mechanism of action of antibiotics. Because it has an apparently low activity in vitro and a higher activity in vivo, it may be helpful in the study of the mechanism of action of these drugs. The drug may find considerable usefulness in tuberculosis if the studies now in progress should prove to follow the preliminary studies that have been completed. A total of 37 cases of tuberculosis were treated at the Metropolitan Hospital in New York in the preliminary work done by Epstein et al.[2] Twenty-nine of these were old chronic cases while 8 were virgin cases. Excellent results were obtained in practically all cases. The 29 cases that had been pronounced failures on intensive prior therapy showed impressive improvement and similar results were obtained with the 8 virgin cases. The patients became less toxic shortly after treatment and temperatures dropped to normal. Weight gains of from 25 to 30 pounds were shown in some cases. All cases showed some weight gain. No serious toxic manifestations were encountered and Epstein et al inferred from their data that cycloserine is a potent antitubercular antibiotic.

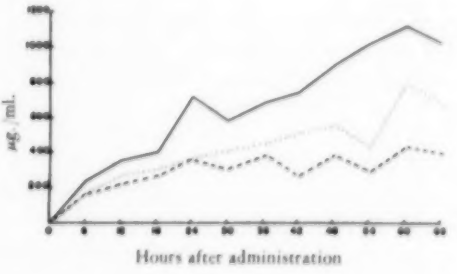

FIG. 7. Urine concentrations of cycloserine following divided oral doses. ———750 mg. every six hours; · · · · 500 mg. every six hours; – – – 250 mg. every six hours.

The over-all results with cycloserine, although preliminary, are quite provocative. The low in vitro activity with a paradoxically high in vivo activity may be of help in explaining the mechanism of action of antibiotic drugs. There is some indication that the drug may be interfering with a common enyzme system or blocking a common metabolic pathway of a wide variety of microorganisms. Even though high blood concentrations are obtained with 1 Gm. daily, these appear to be inadequate because of the low in vitro activity of the drug. It makes one wonder whether the drug stimulates the production of physiologic conditions in the host, which result in an unsafe environment for development or multiplication of microorganisms. Possibly cycloserine stimulates the production of humoral factors that act with the drug in combating infections. Regardless of the future outcome of the studies on cycloserine, the studies to date indicate the need for further intensive clinical and laboratory investigations in an attempt to elucidate the mechanism of its action.

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Carbomycin

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ISOLATION AND CHEMICAL PROPERTIES

Carbomycin* was described by Tanner and his colleagues[1] in 1952 as a crystalline, monobasic substance, which was obtained from broths produced by several strains of *Actinomyces* isolated from different soil samples. The strain of *Streptomyces* that they used in their study was identified as *Streptomyces halstedii*. It was reported to grow luxuriantly under submerged anaerobic conditions and also to grow on several media of organic composition, from which the antibiotic was obtained by conventional methods.

Carbomycin was recovered as slender, white, blunt-ended, needle-shaped crystals of the free base. The free base readily forms acid salts. The base melts with decomposition at 199.5 to 200.5 C. It contains carbon, 59.0; hydrogen, 8.1; and nitrogen, 1.7, and has a neutral equivalent of approximately 860. The base dissolved in chloroform (c, 1%) has an $[\alpha]_D^{25} = -58.6°$. In the ultraviolet region the base exhibits a single absorption maximum at 240 mμ (9.4 mg. in 100 ml. of ethanol). Acid salts of the base, such as the sulfate or hydrochloride, are water soluble; however, the base is only partially soluble in water.

ANTIBACTERIAL ACTIVITY

In Vitro. Tanner and his associates[1] reported that carbomycin is principally active against gram-positive microbes and has little or no activity against the commonly encountered gram-negative organisms. Carbomycin also possesses inhibitory activity against some of the rickettsiae and the large viruses. These investigators reported that the gram-positive microbes, *Micrococcus pyogenes*, *Bacillus subtilis*, *Streptococcus faecalis*, and *Streptococcus viridans*, were inhibited by as little as 0.19 μg./ml. of carbomycin. The gram-negative microbes, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*, were relatively resistant, 100 or more μg./ml. of carbomycin being required to inhibit them.

Finn and Kane[2] also reported in vitro studies on the activity of carbomycin. They found that 25 strains of *M. pyogenes* were inhibited in a range of from 0.3 to 2.5 μg./ml. and that 25 strains of enterococci were inhibited in a range of from 0.15 to 2.5 μg./ml. However, they were able to obtain serum concentrations of only 0.04 to 0.32 μg./ml. in patients who were receiving 3 to 6 Gm. of the antibiotic per day. Difficulty in obtaining adequate serum levels of any new chemotherapeutic or antibiotic agent in humans obviously is a serious drawback.

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* The trade name of Chas. Pfizer & Co. for carbomycin is Magnamycin.

English and his colleagues[3] reported rather extensive in vitro studies of carbomycin. The sensitivity of various microorganisms to this antibiotic was determined by the commonly accepted serial dilution technique. *M. pyogenes*, *B. subtilis*, and *Str. faecalis* were found to be quite sensitive to the action of carbomycin. The gram-negative microbes, *Aerobacter aerogenes*, *E. coli*, *P. vulgaris*, *Ps. aeruginosa*, *Salmonella typhosa*, *Salmonella paratyphi* A, and *Salmonella paratyphi* B all were found to be relatively resistant. *Klebsiella pneumoniae* and *Candida albicans* also were found to be resistant. *Neisseria catarrhalis* was found to be extremely sensitive. From these studies it is apparent that, like erythromycin, carbomycin is a highly selective, rather than a broad-spectrum, type of antibiotic. English and his associates[3] also reported that the activity of carbomycin was not altered appreciably by the presence of human serum. It was further evident that carbomycin is primarily a bacteriostatic agent, although in certain concentrations it possesses bactericidal activity. Studies on the development of resistance in vitro to carbomycin indicated that the resistance pattern shown by carbomycin is comparable to that of penicillin. Resistance is gained slowly by step-wise increments. These studies further indicated that there was little or no cross resistance between carbomycin and other antibiotics commercially available at the time of the report. However, studies, which will be mentioned later, clearly indicated that cross resistance does occur between carbomycin and erythromycin. That carbomycin was more active in vitro against the enterococci than was penicillin or dihydrostreptomycin also was evident from this report.

Seneca and Ides[4] reported some in vitro studies on the activity of carbomycin against certain protozoa and spermatozoa. They found *Trichomonas vaginalis* to be relatively resistant to the action of carbomycin, 250 μg./ml. being required to inhibit it. They also investigated the in vitro sensitivity to carbomycin of *Endamoeba histolytica* and the organisms responsible for leishmaniasis and trypanosomiasis and concluded that these organisms were sufficiently sensitive to this antibiotic to warrant its clinical trial in the treatment of amebiasis, leishmaniasis, and trypanosomiasis. These investigators also reported that human spermatozoa were immobilized in 44 minutes in the presence of 10 mg./ml. of carbomycin. In more dilute concentration, for example, 10 μg./ml., carbomycin had practically no effect on the mobility of spermatozoa.

Gorzynski and Neter[5] determined the in vitro susceptibility of 10 strains of *Pasteurella multocida* to carbomycin, using the tube-dilution method. The organism was found to be quite sensitive to this antibiotic. This is an interesting example of a gram-negative bacillus that is sensitive to the action of carbomycin, which for the most part is active chiefly against gram-positive microbes. In this respect there is a close similarity between carbomycin, erythromycin, and penicillin.

In Vivo. English and co-workers[6] carried out studies to test the in vivo activity of carbomycin against a variety of gram-positive microorganisms, particularly those that had become resistant to one, several, or all of the following antibiotic agents that were then commercially available: penicillin, dihydrostreptomycin, oxytetracycline, chlortetracycline, chloramphenicol, polymyxin B, and bacitracin. (Erythromycin was not commercially available at that time.) Experimental infections in

mice were produced by the intraperitoneal inoculation of 0.5 ml. of the standardized culture suspended in 5 per cent hog gastric mucin. Staphylococcal and pneumococcal infections were established. In every instance the untreated infection proved to be fatal within 48 hours. Carbomycin was administered by the subcutaneous or intraperitoneal route in divided doses.

The antibiotic-resistant infections due to *M. pyogenes* required 50 mg. of carbomycin per Kg. of body weight for 100 per cent protection when the antibiotic was administered by the subcutaneous route. Carbomycin protected 100 per cent of the mice from this infection when administered intraperitoneally in a total dose of 40 to 50 mg./Kg. Twenty mg./Kg. of carbomycin administered subcutaneously protected mice infected with antibiotic-sensitive strains of *M. pyogenes*. When carbomycin was administered intraperitoneally in amounts of 10 to 20 mg./Kg., 100 per cent protection was afforded. Five mg./Kg. of the antibiotic administered intraperitoneally protected 80 per cent of the mice infected with antibiotic-sensitive strains of *M. pyogenes*.

It was further evident from the report by English and his colleagues[6] that 30 mg./Kg. of carbomycin administered subcutaneously protected 100 per cent of mice against experimental streptococcal infections. In the same experiment 100 per cent protection was afforded by 20 mg./Kg. of penicillin administered intraperitoneally. All mice were protected against experimental pneumococcal infections by carbomycin administered intraperitoneally, 60 mg./Kg. A comparable experiment with penicillin showed 100 per cent protection with 40 mg./Kg. when the route of administration was either intraperitoneal or subcutaneous. In other words, penicillin was a little more active than carbomycin against this strain of pneumococcus in mice.

Wong and his associates[7] reported studies on the activity of carbomycin against some viral and rickettsial infections in ovo (embryonated hens' eggs) and in vivo (mice and guinea pigs). Most of their studies were carried out using crystalline carbomycin hydrochloride. In the in vivo experiments administration of the antibiotic, in general, was initiated 24 hours after infection, intraperitoneally, subcutaneously, or orally, and was continued once a day for five to seven days. It was concluded from these studies that carbomycin possesses activity against the following rickettsiae and viruses in ovo: *R. prowazekii*, *R. typhi*, *R. akari*, *R. tsutsugamushi*, *R. rickettsii*, *R. conorii*, North Queensland tick typhus, *Coxiella burnetti*, and psittacosis, ornithosis, lymphogranuloma venereum, human pneumonitis, feline pneumonitis, and sporadic bovine encephalomyelitis viruses. It was further concluded that carbomycin exhibited therapeutic activity after either oral or parenteral administration in mice infected with psittacosis, rickettsialpox, and scrub typhus and also in guinea pigs infected with epidemic typhus and Rocky Mountain spotted fever. Carbomycin was found to be less effective against murine typhus infections in mice than it was against the other rickettsial infections already mentioned. Carbomycin appeared to have little or no effect against experimental infections owing to herpes simplex, encephalomyelitis, rabies, vaccinia, and poliomyelitis type II viruses. Carbomycin compared favorably with chlortetracycline and was more effective than oxytetracycline, erythromycin, or chloramphenicol in the treatment of experimental infections owing to *R. tsutsugamushi*. Carbomycin also was

found to be effective in the control of experimental infections owing to the virus of psittacosis.

Cross Resistance and Synergism. From the reports heretofore mentioned, it was evident that little or no cross resistance existed between carbomycin and the other then commercially available antibiotics. However, it soon became evident that in some respects erythromycin and carbomycin were similar. For example, Finland and his colleagues[8] pointed out that the antibacterial spectra of these two antibiotics were closely parallel. Both substances are highly active against gram-positive and gram-negative cocci, are moderately active against strains of *Hemophilus*, and are essentially inactive against coliform and enteric bacilli. Another significant observation made by Finland and his associates is that, on a weight for weight basis, erythromycin usually is from 4 to 16 times more active than carbomycin against susceptible strains of bacteria. It was further evident from their studies that repeated subcultures of *M. pyogenes* and of certain strains of streptococci in the presence of increasing concentrations of either of these antibiotics resulted in fairly rapid and marked increase in resistance not only to the antibiotic to which it was exposed but also to the other. From that time on it was apparent that cross resistance existed between these two antibiotic agents.

Further evidence to support the fact that carbomycin paralleled erythromycin in its activity against staphylococci and streptococci was reported by Fusillo and coworkers.[9] They also pointed out that, on a weight for weight basis, slightly more carbomycin than erythromycin was required to inhibit sensitive organisms. From their studies it was evident that cross resistance existed between these two antibiotics.

Barr and his associates[10] reported studies that suggested that there appears to be an antagonistic effect between carbomycin and two other antibiotics—bacitracin and tyrothricin. They further reported that polymyxin B and carbomycin, which are active against different organisms, exhibited no antagonism. They suggested that a combination of carbomycin and polymyxin would increase the spectrum of the combined product.

Seneca and Bergendahl[11] reported interesting observations on the synergistic amebicidal effect of tetracycline, oxytetracycline, and carbomycin on cultures of *E. histolytica*. After the inhibitory amount of each of these antibiotics had been determined, their activity in combinations was studied. They found a fourfold increase in the inhibitory effect when equal amounts (by weight) of tetracycline and oxytetracycline were combined and a twofold increase when either tetracycline or oxytetracycline was combined with carbomycin.

The practical importance of these studies dealing with cross resistance, antagonism, and synergism is apparent. For example, in the event that one were using erythromycin in the treatment of an infection caused by a microorganism that developed resistance to this antibiotic, shifting to carbomycin would be unlikely to improve the clinical result. However, whether or not the antagonism and synergism noted in experimental infections is of clinical significance cannot be definitely stated on the basis of data available at the time of this writing.

ABSORPTION, DIFFUSION, AND EXCRETION

A significant observation made in the early studies carried out on carbomycin was that high concentrations of the antibiotic failed to appear in the serum, even after fairly substantial amounts of it were administered. Nevertheless, Finn and Kane[7] pointed out that occasionally they noted a favorable clinical response to carbomycin therapy despite failure to obtain levels of the antibiotic in the serum, which were in the range of the minimal inhibitory concentration in vitro. The explanation for this is probably, as was subsequently reported by Wong and his colleagues,[7] that unlike many other antibiotics, carbomycin, although present only in low concentration in the blood, is present in high concentration in various body tissues.

English and his associates[12] carried out studies in rabbits to determine the absorption patterns of both the hydrochloride and the sulfate salts of carbomycin after administration of single doses orally, intramuscularly, or intravenously. Concentrations of carbomycin in the serum were determined by the twofold, serial dilution method similar to the Rammelkamp[13] method used for assay of other antibiotics. They modified this technique, however, so that assays were carried out in the presence of a constant amount of serum (25 per cent). The results of their studies were essentially as follows: Detectable levels of carbomycin were found in the serum of rabbits after intramuscular, oral, or intravenous administration of either carbomycin hydrochloride or carbomycin sulfate. Maximum serum concentrations of carbomycin were detected within 30 to 60 minutes after its administration by any of the three routes employed. In general, the serum concentration was proportional to the dose administered. After the concentration of carbomycin in the serum reached its peak, it declined rapidly; however, small amounts of the antibiotic still could be detected eight hours later. Detectable levels of carbomycin were found in the urine of rabbits within 30 to 60 minutes after administration of the antibiotic by any of the three routes used. Maximum concentrations of carbomycin in the urine occurred sometime between one and five hours after administration of the antibiotic. There was no significant difference in urine concentrations noted following administration of the various forms of carbomycin. Only small percentages of the total amount of the antibiotic administered could be accounted for at any one time in the urine.

English and co-workers[12] also found detectable levels of carbomycin in the sera of 12 patients to whom they administered the antibiotic either intramuscularly or orally in doses of from 3 to 18 mg./Kg. of body weight. Slightly higher serum concentrations were obtained when carbomycin was administered orally in conjunction with a meal than when it was administered between meals.

Brainerd and his colleagues[14] also reported some studies on the clinical pharmacology of carbomycin. They administered single doses of the antibiotic to 46 hospitalized patients. Nineteen of these patients were suffering with a variety of acute and chronic diseases except those of the liver and biliary tract, 6 had liver disease without jaundice and 21 had jaundice. Samples of blood for assay of serum concentrations of carbomycin were obtained at intervals of 1 to 24 hours following the administration of carbomycin, either 2 Gm. orally or 0.5 Gm. intravenously. They also determined the concentrations of carbomycin in specimens of urine, stool, and

bile and in cerebrospinal and ascitic fluid. Determinations of the carbomycin content of body fluids were performed by a serial tube-dilution method, using *Streptococcus pyogenes* as the test organism. In the subjects who had neither jaundice nor disease of the liver, they found low serum concentrations that often did not persist for more than six hours. Serum concentrations of carbomycin in these patients were unexpectedly low as compared to those that were obtained following administration of chlortetracycline given in smaller doses. In the jaundiced patients who received carbomycin they found high serum concentrations of the antibiotic, which persisted for 12 or more hours. These investigators confirmed the previous reports that renal excretion of carbomycin is slight. They found that the antibiotic was excreted promptly in high concentrations in the bile. They were of the opinion that the low serum concentrations of carbomycin observed in nonjaundiced persons were due principally to rapid excretion of the antibiotic in the bile. They also reported that carbomycin appeared readily in the ascitic fluid but did not appear at all in the cerebrospinal fluid within six hours after its administration in persons with noninflamed meninges.

English and his colleagues[15] carried out determinations of the tissue distribution of carbomycin following its administration either intravenously or orally to rabbits. At appropriate intervals of time after administration of the antibiotic, specimens of blood and spinal fluid for assay were obtained simultaneously. The animal then was sacrificed and samples of various tissues obtained, including spleen, pancreas, kidney, liver, intestine, muscle, lung, brain, heart, and regional lymph nodes. They also obtained specimens of bile, urine, and stomach and intestinal contents. Thirty minutes after the intravenous administration of 100 mg. of carbomycin per Kg. of body weight antibiotic activity was found in 17 of the 20 tissues, contents, and body exudates studied. After three hours nearly all of the materials studied showed activity equal to or greater than that in the serum. Two hours after the oral administration of 200 mg. of carbomycin per Kg. of body weight antibiotic activity was found in 20 of the 22 materials studied. In nearly every instance the content in the tissues was greater than that in the serum. After four hours, at which time little or no activity could be demonstrated in the serum, 20 of the 22 materials studied still showed some carbomycin activity. These findings are in accord with the statement made by Wong and his associates,[7] which was already mentioned. Little or no activity could be demonstrated in the brain, spinal fluid, or muscle.

CLINICAL USES

Inability to obtain high concentrations of carbomycin in the serum probably has been a major factor in discouraging widespread clinical use of this antibiotic. Nevertheless, carbomycin has been employed in the treatment of a limited number of infections, chiefly respiratory and urinary infections.

Respiratory Infections. Manning and his colleagues[16] used carbomycin in the treatment of 23 patients suffering with infections of the upper respiratory tree owing to *Str. pyogenes*. Nineteen of these 23 patients had exudative tonsillitis, 3 had pharyngitis, and 1 had scarlet fever. Most of the patients received 500 mg. of car-

bomycin every six hours orally, although a few received only 200 or 300 mg. Throat cultures from 18 of 22 patients were negative 48 hours after carbomycin therapy was begun. Of the 23 cases, results were regarded as failures in 2 and as a clinical relapse in 1. In general, a favorable response to carbomycin therapy occurred in patients suffering with streptococcal sore throat within 18 to 48 hours after initiation of treatment. However, a significant number of patients manifested a rebound of low-grade fever for an additional 24 to 68 hours. The clinical response appeared to be considerably less rapid than that which occurred in patients who received penicillin. It was concluded that carbomycin did not appear to replace any of the more established antibiotics in the treatment of infections due to *Str. pyogenes*. It should be pointed out that failure of patients to respond to carbomycin therapy certainly could not be explained by lack of sensitivity of the infecting organism to this antibiotic.

Finland and his associates[17] administered carbomycin to 31 patients suffering with pneumococcal pneumonia. Most of the patients received the antibiotic orally, but 2 received it intramuscularly. In general, the clinical results were distinctly inferior to those observed with other antibiotic agents. In 12 patients it was believed that the continuation of carbomycin therapy was not justified, and penicillin was given to them in the hope of terminating their infections. In only about half of the patients could the response to carbomycin therapy be considered favorable. Moreover, a dramatic clinical response, like that seen after the administration of penicillin, chlortetracycline, oxytetracycline, or erythromycin, was observed infrequently in the carbomycin-treated patients. Here again it is well to emphasize that lack of clinical response could not be attributed to absence of sensitivity of the infecting organism to the antibiotic. These investigators noted that, even after maximum tolerated doses of carbomycin were administered orally, concentrations of the antibiotic in the serum were irregular and generally lower than those required to inhibit most of the common pathogenic microbes.

Hewitt and Wood[18] reported some favorable clinical responses to carbomycin therapy in patients suffering with infections caused by pneumococci and *Str. pyogenes*. However, the bacteriologic results in a number of these cases were less striking than would have been expected from penicillin therapy. The dosage of carbomycin that they recommended was 500 mg. by the oral route every six hours. Bunn and Cook[19] reported on the use of carbomycin in the treatment of 8 patients who had pneumococcal pneumonia. Four of these patients responded satisfactorily, and in a fifth patient the pneumonia cleared after six weeks. There were 3 clear-cut treatment failures, both bacteriologically and clinically. Field and Taylor[20] also reported some clinical studies on the use of carbomycin in the treatment of pneumococcal pneumonia. The antibiotic was administered orally in amounts of 500 mg. every six hours to 14 patients, and 14 other patients received an initial dose of 1 Gm. followed by 250 or 300 mg. every six hours. Twenty of the 28 patients treated responded satisfactorily.

On the basis of these reports it seems reasonable to conclude that carbomycin has not proved highly effective in the treatment of pneumonia.

Urinary Infections. From the studies on absorption and excretion of carbomycin,

it was evident that carbomycin was not readily excreted, at least not in a biologically active form, in the urine. For this reason alone one would not expect carbomycin to be highly effective in the treatment of infections of the urinary tract.

Trafton and his colleagues[21] reported good results using carbomycin in the treatment of a limited number of infections of the urinary tract due to enterococci, which were sensitive to the antibiotic. However, in a subsequent report Trafton and Lind[22] pointed out that complete cure occurred in only 7 of 52 patients. Thirty patients, although sensitive enterococci were eliminated from their urinary tracts by carbomycin therapy, subsequently developed infections due to gram-negative bacilli. Hewitt and Wood[18] reported on the use of carbomycin in the treatment of 6 patients suffering with chronic urinary infections. *Str. faecalis* was isolated in pure culture in 4 patients and *M. pyogenes* in 2. No definite symptomatic improvement occurred in these cases. Enterococci were eradicated from the urine in 2 of the 4 patients, but persisted in 2. *M. pyogenes* remained in the urine after treatment with carbomycin, but disappeared temporarily after oxytetracycline therapy.

Miscellaneous Infections. Carbomycin has been employed in the treatment of a few infections other than those already discussed.

Sodeman and Jung[23] administered the antibiotic to 4 patients who had acute amebic colitis. Symptoms were controlled and amebic ulcers in the colon promptly healed. In one of these patients it was reported that oxytetracycline previously had failed to control the infection. Hewitt and Wood[18] also reported good results using carbomycin in the treatment of 5 patients suffering with intestinal amebiasis. One of these patients had bloody diarrhea, which completely disappeared within 48 hours after initiation of carbomycin therapy. Cysts and trophozoites disappeared from the feces of all 5 patients within 72 hours after initiation of treatment. The feces of 4 patients re-examined six weeks after treatment still were negative for *E. histolytica*. One patient had persistent fever and pain and tenderness in the right upper quadrant of the abdomen despite eradication of the organism from the feces. Chloroquine therapy controlled the fever and abdominal findings; however, relapse occurred later. At that time a large hepatic abscess was drained, but the abscess was sterile on culture and no amebae were demonstrated by either direct or histologic examination. These preliminary studies suggest that carbomycin is of value in the treatment of intestinal amebiasis. This is not surprising in view of the fact that large concentrations of the antibiotic are present in the intestinal tract after its oral administration. Needless to say, therapeutic results in the treatment of amebiasis are not dependent upon attaining bacteriostatic or bactericidal concentrations of an antibiotic in the serum.

Hewitt and Wood[18] employed carbomycin with uniformly poor results in the treatment of 5 patients who were suffering with subacute bacterial endocarditis. They also reported that the response to carbomycin therapy of patients who had staphylococcal sepsis was not striking.

Kutscher and co-workers[24] were impressed with the value of carbomycin in the treatment of 5 patients with oral infections. They also used the antibiotic successfully as a prophylactic agent in the mass extraction of chronically infected teeth in 8 patients.

Manning and his colleagues[16] employed carbomycin in the treatment of 5 patients suffering with acute gonorrheal urethritis. These patients received 500 mg. of the antibiotic every six hours for 48 to 72 hours. Carbomycin failed to cure this infection in any of these patients.

REACTIONS OF TOXICITY

It was evident from the studies of Gardocki and his associates[25] that carbomycin has a low degree of toxicity in experimental animals. Daily intravenous injections of the antibiotic for five days were well tolerated by dogs. Daily oral or intramuscular administration of carbomycin for as long as 20 weeks produced no untoward systemic symptoms in dogs. Rats fed a diet containing carbomycin for 17 weeks continued to grow at a rate similar to that of controls. Cats which received daily intramuscular injections of carbomycin for nine weeks revealed no evidence of damage to the eighth cranial nerve. The antibiotic was found to have no sensitization effect on guinea pigs.

In a study of the influence of carbomycin on the clotting time of whole blood of rabbits, Macht and Kremen[26] found the antibiotic to have no thromboplastic properties.

In other words, studies in experimental animals which have been reported lead one to the conclusion that carbomycin is a relatively safe antibiotic.

Reports of studies of this antibiotic in humans indicate that it is of low toxicity, as measured by the lack of production of any serious systemic reactions. To date, the toxic effects of carbomycin in humans have consisted almost entirely of gastrointestinal irritation after full therapeutic doses of the antibiotic have been administered orally. Gastrointestinal irritation, in the form of nausea, diarrhea, and, occasionally, vomiting, has been reported in almost one fourth of the patients receiving carbomycin. The incidence of symptoms due to gastrointestinal irritation reported by Trafton and Lind[22] was 25 per cent. Manning and his colleagues[16] reported that gastrointestinal irritation occurred in 4 of 23 patients to whom they administered carbomycin. The incidence of nausea, vomiting, or diarrhea reported by Hewitt and Wood[18] was slightly less than that already stated. One or all three of these symptoms occurred in only 5 of 51 patients who received carbomycin. However, these investigators reported that skin eruptions occurred in 3 patients on the third, fifth, and sixth days of treatment. In one of these patients in whom a macular rash appeared, the patient had had scleroderma and a prevous history of sensitivity to drugs. A rather extensive desquamation occurred in this patient. Hewitt and Wood[18] also noted that somnolence and lethargy appeared in 2 patients during carbomycin therapy. However, both of these patients were elderly and had severe pneumonic processes. Therefore, the reaction more likely was associated with the ages of the patients and the severity of their infections than with the use of carbomycin.

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EDITORIAL SURVEY

Health Through Travel

Time was when travel by stagecoach exposed one to bodily contusion, mental anguish, insanitary inns, and antisocial highwaymen. As it was proved at the First International Symposium on Health and Travel, organized by the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS, times have changed.

The bad old days were picturesquely described by **Dr. Martí-Ibáñez** in a historical survey of physician-travelers through the ages. The first of the many peripatetic physicians was Democedes of Croton who, in the sixth century B.C., wandered extensively throughout Asia. History does not tell us whether this intrepid Greek suffered from seasickness and camel-sickness, but it is more than likely that he did. The sailors of Magellan, Columbus, and Drake, although hardy men, certainly hung over the rail as piteously as any modern sea traveler. Besides which they had to endure such discomforts as scurvy, inadequate food, "sailor's vapors," and sundry unspecified fevers. In those days also, travelers were used as unwitting vehicles by the microorganisms of cholera, plague, and smallpox. While olden times may seem romantic in retrospect, Dr. Martí-Ibáñez brought us sharply down to medical reality.

But if times have really changed for the better, travel still poses many problems for the inexperienced voyager. How about air- or seasickness? What about the children? How will a long trip affect my heart, stomach, asthma, varicose veins? Will I be in danger of picking up some exotic germ? All these questions were competently answered by a panel of experts at this Symposium on Health and Travel and judging by the response of the audience and of the press, they aroused a great deal of interest.

There was sound advice to pediatricians and geriatricians from **Dr. Kugelmass** and **Dr. Foley.** Most children love to travel, if only to break the monotony of their daily routine and to escape a little from domineering parents, Dr. Kugelmass explained. Children feel "at home in motion in other lands," and a voyage can help develop their self-reliance. As for the aged, Dr. Foley assured us that they need not worry. From his own experience in a war prison camp, he had found that older people adjust better to environmental strain than do younger adults. Their one weakness might be a sluggish circulation, for which Dr. Foley recommended a brisk jaunt now and then to keep the lazy erythrocytes moving. Above all, he warned men of wearing tight garters and advised women to leave off their constricting girdles which were apparently never designed for sitting down.

Practical advice for travelers of all ages was offered in an enlightening talk by **Dr. Alvarez,** himself an inveterate voyager. He admitted that some people are mentally unfitted to travel. They fuss and fume about almost anything, until they finally worry themselves into a heart attack or a bout of dyspepsia. Dr. Alvarez warned against eating heavy meals after a tiring journey, an unwritten precept followed by the humble mule that, unlike some humans, has the good sense to refuse food spontaneously when it is tired. This point was also stressed by **Col. Perry** who advised

us not to rush from an airplane to a restaurant, the sound advice that she also gives to the flying personnel of the United States Air Force.

The fear of infection in foreign lands was thoroughly allayed by **Dr. Loughlin** who informed us that the common diseases are generally much the same abroad as in America. A coryza virus (if such exists) apparently has no strong feelings of nationalism. The regional difference lies in the host. It is quite possible, as **Dr. May** engagingly pointed out, that some forms of immunity are built into the "genotype" of individuals through heredity. This would explain why *Escherichia coli* may bother an American visitor with diarrhea for a day or two, while it leaves the familiar Cockney cheerfully unharmed. As for treatment of what was once called "voyager's flux," we can always fall back on that ancient but no less effective remedy, paregoric.

And what about motion sickness and its precursor, motion sensitivity? A nauseating subject, at best, which was expertly discussed by **Dr. Chinn** and illustrated with statistical slides. Who suffers most from this distressing complaint? Women, and adolescents of both sexes, apparently, though why this should be so is a mystery. Possibly because these two groups are less accustomed to traveling than adult males.

One's position aboard a ship or a plane has a good deal of influence on visceral comfort, it appears. In a ship, the middle is healthier than both ends, if we may be forgiven un-nautical terms. In an airplane, more people get sick when sitting on the left side near the wing. This is believed to be owed to the pilot's preference for banking to port in his maneuvers, with the result that the passenger who suddenly sees the wing dip into a yawning void is understandably discomfited. At any rate, it was reassuring to learn that the incidence of airsickness is lower than that of seasickness, although such statistics may be but cold comfort for the sufferers on both routes.

As for prophylaxis and treatment, Dr. Chinn had some heartening news for everyone. He amused the symposium audience with his catalogue of weird remedies and gadgets that have at various times been recommended for seasickness, ranging from abdominal corsets to an exclusive diet of crackers.

Of the hundreds of drugs that have been ingested and injected to stave off motion sickness, it now appears that the antihistamine group gives the best results in most cases. They go by such melodious trade names as Bonamine, Marezine, and Dramamine. All are effective, though on the evidence Bonamine appears to be the only one that protects a traveler for 24 hours on the strength of one tablet. The others are mostly of the t.i.d. variety. Dr. Chinn emphasized the old adage that an ounce of prevention is worth a pound of cure by pointing out that it is easier to prevent seasickness with the modern drugs than to stop it once it has begun its retching course. The object of a drug should be to obviate the motion sensitivity syndrome, that dreary period when we acquire what Samuel Butler facetiously called the "holy look" of seasickness, retiring from our surroundings to commune queasily with our viscera.

The more cheerful side of sea travel was painted at the symposium by **Dr. Wheeler,** himself at one time a ship's surgeon. From his talk we gathered that while all is well for the passenger, the life of a ship's surgeon is not exactly an easy one. He is responsible for sanitation throughout the ship, down to the last saucer, for quaran-

tine measures, for the crew's fitness, and for the passengers' health. He must be prepared to perform an appendectomy while the sick bay is tilted at an angle of 45 degrees. On top of all that, the harried man must also turn away the wrath of pet lovers who simply cannot understand why their darling pekingese or parakeet should go into quarantine. On the brighter side, Dr. Wheeler convinced us that a sea voyage is an excellent remedy for respiratory tract diseases, hypertension, various neuroses, or simply a fit of the "blues."

The more endocrinologic approach to health and travel was made by **Dr. Jasmin,** an associate of Dr. Hans Selye, who may be called the father of the "stress" concept in psychosomatic medicine. Travel imposes a number of "stressors" on the organism, whether in bodily discomfort or mental anxiety. These set off the first alarm stage in the Selye general-adaptation-syndrome, urging the pituitary gland to stir up the adrenals with ACTH. The defences of the body are all mobilized to counteract the stressor agent, but if this goes on too long the organism will lapse into exhaustion. Dr. Jasmin illustrated this complex mechanism with some admirable pathology slides. Yet having said all that, he comforted us with the thought that most of the stresses set up by travel are stimulating and therefore beneficial. They goad our endocrine system into activity, but not enough to harm us.

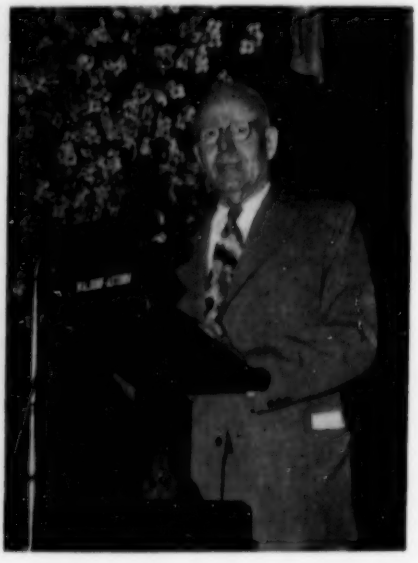
Finally, the symposium having disposed of all the problems of earthly and atmospheric travel, **Dr. Strughold** destroyed our peace-of mind by posing the many problems that man will encounter when he starts traveling to the moon and other interstellar resorts. He spellbound his audience with fascinating slides of "sealed chambers" in which space-travelers will carry their terrestrial atmosphere with them. What they will do when they reach their destination is a point that Dr. Strughold left open.

Before reaching a happy landing, the space vehicle will have to fly through showers of meteors, for which engineers have thoughtfully provided the craft with "meteor screens." The occupants will also be bombarded by cosmic-ray particles with intensities as high as 2,000 million electron volts, but no doubt this problem also will be solved in due course. As for gravitation, Dr. Strughold consoled us with the information that once we are removed from the pull of earthly gravity we will probably experience the same euphoria that comes from ingesting two or three cocktails.

This Symposium besides accomplishing other aims helped to destroy the myth of the "good sailor" as contrasted with the groaning wretches below decks. Every one at some time or another has experienced the queasiness of motion sensitivity, whether in a train, a motor car, a ship, or an airplane. With the help of the simple precautions advocated at the meeting and the miraculous new drugs, every one can now travel in comfort. We are thus tempted to paraphrase Stevenson's famous dictum as: To travel healthily is a better thing than to arrive.

Highlights of The First International Symposium on Health and Travel

Dr. Félix Martí-Ibáñez, Moderator, (above) opened the First International Symposium on Health and Travel with his speech, "The Physician as Traveler." Seated from left to right are Dr. Hubertus Strughold, Col. Miriam Perry, Dr. Herman Chinn, Dr. I. Newton Kugelmass, Dr. Elmer Loughlin, and Dr. Gaetán Jasmin. Dr. Herman I. Chinn (below, left) presented a paper on "Travel and Motion Sickness." Seated next to him is Dr. William L. Wheeler, Jr., Medical Director of W. R. Grace and Company, who delivered a paper on "Sea Travel and Health." Dr. Walter Alvarez (below, right) advised the audience on "When Sick People Travel."



Dr. Hubertus Strughold (top) discussed the problems of space flight and illustrated his speech with a slide of the experimental sealed chamber at the USAF School of Aviation Medicine, Randolph Field, Texas. During the Question and Answer Period that followed the presentation of the papers at the Health and Travel Symposium, Dr. Martí-Ibáñez called on members of the panel to answer queries from the audience: Dr. Wheeler (above) explained the duties and responsibilities of the ship's surgeon. Dr. I. Newton Kugelmass (right) noted pediatrician, professor, and author, spoke on "When Children Travel."

Dr. Wheeler (top, left) recommended sea travel for worried, neurotic, or overworked persons. Colonel Miriam Perry (top, right), Chief of the Women's Medical Specialist Corps, stressed the importance of nutrition in maintaining flight efficiency and safety, as well as health. Dr. Chinn, (above) stated that almost everyone can protect himself from motion sensitivity with the new drugs. The importance of the psychologic day-night cycle after global flights and global space flight was emphasized by Dr. Strughold (below).

Dr. Strughold (above) answered questions from the audience, presented by Dr. Martí-Ibáñez, Moderator, on interplanetary space travel. Dr. Jacques May (right), Head of the Medical Geography Department, American Geographical Society, defined disease as a response of living tissue to environmental stimuli and therefore conditioned by many geographical factors. Dr. Wheeler (below) traced the history of scurvy in his speech, "Sea Travel and Health."

FELIX MARTI-IBAÑEZ, M.D.
International Editor of
INTERNATIONAL RECORD OF MEDICINE
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The Physician as Traveler

INTRODUCTION TO THE FIRST INTERNATIONAL SYMPOSIUM ON HEALTH AND TRAVEL

It is both a pleasure and an honor to greet on behalf of the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS the distinguished guests and audience of this First International Conference on Health and Travel.

We have brought together here a brilliant array of internists, pediatricians, specialists in aeronautical, naval, and space medicine, medical geography and physiology to discuss what happens to *Homo sapiens* today when he is transported out of his customary environment by plane, train, boat, automobile or submarine into new lands, new seas, and new skies. We shall also study what happens to man under such circumstances at different times in his life, in health and in sickness.

Man is the most restless of all living beings. From the very beginning of his existence man has incessantly roamed the earth, at first on foot and later on horseback. One day man invented motor-propelled vehicles which helped him to conquer the earth and the seas—finally he soared into the air in his supreme longing to conquer space.

Living is traveling *par excellence*. Life itself is a stormy voyage from the shores of light marking our birth to the shadowed threshold of death, when we cross over the line into the land of mystery. The Greek Argonauts symbolized this concept of

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The Physician as Traveler was presented at The First International Symposium on Health and Travel by Dr. Martí-Ibáñez, who served as chairman. The papers delivered by Doctors I. Newton Kugelmass, William T. Foley, and Elmer H. Loughlin are also presented in this issue of the INTERNATIONAL RECORD OF MEDICINE. The August and October issues will contain papers by the following participants in the Health and Travel Symposium: Dr. Walter C. Alvarez, Dr. Herman I. Chinn, Dr. William L. Wheeler, Dr. Gaetán Jasmin, Col. Miriam E. Perry, Dr. Jacques May, Dr. Hubertus Strughold, and a summation by Dr. Martí-Ibáñez.

life as incessant travel when they said: "The essential thing is not to live; the essential thing is to travel."

When man is confined to one point in space because of a lean pocket or for other reasons, he travels vertically on the wings of his inspiration like the mystics and poets, or in an armchair like Jules Verne and his readers, or through time on the Pegasus of his art, like artists of all ages.

But here we shall study travel as a physical displacement through time and space because traveling is the characteristic *modus vivendi* of modern man. In prehistoric times man traveled only when impelled by fear or hunger. Primitive man traveled when threatened by the icy avalanches of invading glaciers or the frightful droughts that turned the earth into sterile ground, by the invasion of fearful monsters or floods, the approach of enemy tribes or geologic cataclysms. Later, in the ancient world, traveling became the living expression of the learned man's longing to learn more. Ancient Greece differentiated between sedentary and traveling physicians or *periodeutes* as the latter were called.

The medieval world witnessed great waves of migration resulting from war or invasion, contrasting the restless life of the knight errant and the crusader with the sedentary life of the scholar, the monk or the scribe in the monasteries, those stone coffers closed to everything from the outside world but the sun pouring through the stained-glass windows in a cascade of sparkling colors.

The Renaissance marked the beginning of the great explorations, among them the travels of Marco Polo in quest of the riches of Kublai Khan, perhaps for many reasons the most important historical gesture and an unequivocal expression of Renaissance man's yearning to discover what lay beyond the confines of his land, to venture beyond the edge of darkness of the world, then considered as a flat, saucer-like disk. It is not until the seventeenth century, however, that we find man dedicating himself to a methodical fulfillment of his yearning to explore every room and corridor of the planet of which he knew but a tiny parlor.

By the nineteenth century the great land and sea expeditions had covered almost the entire earth so that little was left to explore in our century. Hence, the reason, as Lawrence of Arabia prophesied, that twentieth century man was overcome by a passionate longing to explore his planet vertically, as if to compensate for twenty centuries of horizontal explorations. He descends in the endless depths of the ocean with Picard and soars into the limitless stratosphere.

Meanwhile, thinkers, mathematicians, and poets have continued to make the greatest voyage of all, through space as well as through time, traveling astride a poem, a philosophy, or a scientific theory. Even the ordinary individual keeps pace with the great explorations. Travel today is a necessity for some, an integral part of the work of many, and the ambition of every one. As Chesterton foresaw, the modern world has expanded under the microscope, but it has contracted with the airplane. Thanks to the plane—some countries have made a direct transition from mule to airplane!—travel has become so rapid and countries are brought so close that what happens in one place resounds throughout the world.

The best part of traveling, or *dépaysement*, as the French say, is not the rest from work that it affords, for all travel involves certain tasks more or less burdensome,

but the fact that it tears us away from our responsibilities. The traveler lives for himself, not for his family or his habitual milieu. A new country is a play in which we cease to be participants and become onlookers. A trip is not only a physical displacement in space but also a leap into freedom, guaranteed – except for politicians or screen stars—by blessed anonymity.

As the most distinguished physician-writer of our time, Somerset Maugham, said in his travel book, *The Gentleman in the Parlour*, nobody has expressed the joy of travel better than Hazlitt in his essay *On Going a Journey*: "Oh! It is great to shake off the trammels of the world and of public opinion; to lose our importunate, tormenting, everlasting personal identity in the elements of nature, and become the creature of the moment, clear of all ties; to hold to the universe only by a dish of sweetbreads and to owe nothing but the score of the evening, and no longer seek for applause and, meeting with contempt, to be known by no other title than the 'gentleman in the parlour.' "

The physician could not resist this lure of travel, which has today become an accessible pleasure and even a necessity. Tied down to his patients or his hospital like a galley slave to his oar, the physician has perhaps suffered more than others from the impact of *Wanderlust*. The pages of history bear the names of many physicians turned explorers, travelers, and adventurers who carried their science and their dreams to the four corners of the earth.

We can appreciate what travel has meant to the physician and what the physician has meant to travel simply by mentioning two books, one medical, the other a masterpiece of literature. One is the first treatise on public health compiled for the *periodeutes*, or wandering physicians, by Hippocrates (460–370 B.C.) under the title *Air, Water and Places*. It contains all kinds of advice on changes of air, water, and environment which might affect the human being. The second book is Jonathan Swift's *Travels Into Several Remote Nations of the World* (1726), a satire for grown-ups which also fascinates children. Lemuel Gulliver tells us that he was a surgeon's apprentice in London and that he had gone to study in Leyden, then one of the most enlightened centers of European medicine. "There," Gulliver says, "I studied physic two years and seven months, knowing it would be useful in long voyages."

Actually, the honor of being the first physician-traveler and explorer belongs to Democedes of Croton (sixth century B.C.), who, according to Herodotus, traveled throughout Asia. Physician to Polycrates, Democedes treated Darius, King of Persia, for a twisted ankle and established a medical link between the learned classical world of democratic Greece and the turbulent world of Asia.

Two basic motives have linked the physician with travel. First, his own desire to move about and acquaint himself with the world in which we live; second, the innumerable medical problems raised by travel in its evolution from the role of something accidental or adventurous into something essential to modern life, problems which stem from the ecologic changes affecting the traveler, who is subject to incessant variations in diet, climate, atmospheric pressure, and other environmental factors.

Paradoxically, in former times travel involved fewer mental and other health risks than it does today. It was slow, on foot or on horseback, as in the case of the

Mongol explorers, or by ship, as in the case of the Greek Argonauts, and the traveler had ample time to become acclimatized physically and mentally to new environments.

The plane, even more than the train or ship, has revolutionized all that. A century ago, traveling by stagecoach, the voyager mentally arrived at his destination days, even weeks, before his poor broken body. Today, the body which leaves New York and in less than twenty hours is in Paris, Brazil, Hawaii, Cairo, or Greenland, arrives at its destination long before the mind has time to adapt itself to the new situation. This anomaly has given rise to several new psychosomatic problems.

Furthermore, advances in locomotion have created new dangers, as nowadays man is not alone to travel—so do disease carriers. A mosquito traveling by plane from Africa to Brazil brought in its wake a malaria epidemic which might have become catastrophic. A bus traveling from Mexico to New York brought, lodged in the body of a sick passenger, the smallpox virus that caused near epidemic in Manhattan. Cattle ticks, plants, rodents, rats, flies, insects, birds, mammals of all species, traveling by auto, rail, ship, and plane, can today spread disease all over the world with the speed of the vehicle carrying them. That is why the World Health Organization tries to cope with problems of disease and to watch over human health on a world-wide scale. Travel may improve or restore a person's physical or mental health, but it does not alter the fact that in travel, one runs the risk of disease or even death. "Where the body goes, there goes death," says an ancient Spanish proverb.

In medieval times frightful epidemics—bubonic plague, cholera, smallpox—followed the great caravan routes. Death galloped on the heels of the interminable processions of pilgrims, crusaders, and nomads who, on foot or on horseback, slowly crossed the burning sands of Asia and Africa. Today combustion motors have contracted the world, shortened our trips, and even freed us from dependence upon weather, and man is no longer the completely helpless victim of winds or storms. The quarantines that protected the eighteenth century traveler have all but disappeared and are applied only in outbreaks of sudden epidemic.

The dangers that threatened sailors and passengers were infinite in the days of wooden ships and men of iron, from the epic saga of Columbus to the bold adventures of Sir Francis Drake's buccaneers. Along with the so-called fevers, a vague label that covered all infections listed in our modern medical textbooks, there were wounds and shock caused by accidents, ship boardings, or naval battles, and malnutrition from insufficient or inadequate food, which was always the same on war ships: hardtack and "mazmorra" on Philip II's galleys, and hardtack and salt pork on British and American frigates. There were also *sailor's vapors*, mental disturbances of the neurotic or frankly psychotic type, which beset seamen during long crossings when they were condemned to a monotonous vitamin-deficient diet and confined in hulks like wooden cells wedged between the endless walls of sea-blue and sky-blue, aggravated by the daily official ration of a half pint of rum customary on British ships.

All these threats of pain, sickness, and even death that haunted travelers in former times have been eliminated thanks to the many physicians who, ignoring the cruel hardships of travel, dedicated themselves to exploring the earth and doggedly spread the art of healing and the science of preventive medicine all over the world. The

honor roll of physician-explorers on land, on sea, and in the air is indeed a blazing page in medical history.*

Among the physician-explorers who bear witness to the perennial fascination of travel for our colleagues we should mention the Portuguese Garcia de Orta, who explored India in the sixteenth century; the surgeon Monkhouse, who overcame scurvy on Cook's expedition to the South Seas in 1769, in which undertaking he was accompanied by Dr. Solander, a physician and naturalist from Upsala; Dr. Walter Rusell, *Doctor of Physicke*, who accompanied Captain John Smith on his explorations of the craggy Chesapeake region; the Scottish surgeon James Bruce (1730–1794), who discovered the origin of the Blue Nile; the Scottish surgeon Mungo Park (1771–1806), who explored Senegal and Kaarta; Dr. Livingstone (1813–1873), the discoverer of the Zambesi River and the Victoria Falls; and the German doctor, Eduard Schnitzer (1840–1892), the fabulous Emin Pasha, hero of the Sudan.

The most famous explorations of Arabia in the nineteenth century were made by men who had studied medicine and practiced it in Arabia as the most effective means of winning the confidence of the Arab tribes: Richard F. Burton (1821–1890), the immortal translator of the "Arabian Nights"; W. G. Palgrave (1826–1888); and C. M. Doughty (1843–1926), who left us his *Travels Through Arabia Deserta* which inspired the saga of Lawrence of Arabia.

It was the naval surgeons who conquered the seas, just as the flight surgeon today shares the credit for the conquest of the skies; naval surgeons such as James Lind, who conquered the scurvy which had caused ten thousand deaths, according to the reports of Admiral Hawkins; Thomas Dover, who discovered on the island of Juan Fernandez, not far from the Chilean coast, the man called Alexander Selkirk who was later immortalized as Robinson Crusoe by Daniel Defoe; Eugene Sue, also famous as a novelist; and last but certainly not least, Tobias Smollett, whose laurel wreath is twined with both medical and literary honors and who "discovered" the French Riviera. Many other naval physicians could be mentioned whose genius dispelled the abysmal terrors once held by the seas.

Having conquered land and sea, man was loath to remain chained to the earth. He longed for wings to carry him higher than eagles fly. Again, physicians were pioneers and heroes in the conquest of the skies. On June 5, 1783, at Annonay near Lyons, the Montgolfier brothers released the first balloon ever to drift through space. The beloved historian, Dr. Victor Robinson, left a brilliant description of this event. The bizarre experiment, forerunner of present-day aviation, was born of the most poetic idea ever conceived in the human mind: what would happen if one of the slow, fat clouds floating through the pale French skies were imprisoned in a bag? Instead of a cloud, the Montgolfiers used smoke to fill their balloon.

A few months later at Versailles, before the astonished eyes of Louis XVI and

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* To those interested in medical explorations I recommend, among the books consulted in writing this address, the excellent monographs on this and related subjects by Doctors Victor Robinson, G. Schaefer, and W. Naumann, and E. H. Ackernecht published in Ciba Symposia (Vol. 2, No. 8, Nov., 1940; Vol. 3, No. 8, Nov., 1941; Vol. 4, Nos. 9 and 10, Dec., 1942–Jan., 1943; Vol. 5, No. 9, Dec., 1943), which are the best summations ever written on the subject.

Marie Antoinette, amid a concourse of powdered wigs and faces and in an aura of scents, there rose a balloon as beribboned and bepainted as a marquise at the royal court; in the basket there trembled a sheep, a cock and a duck, the first living beings ever to ascend into the air by action very different from that of a bird's wings.

And the first human being to ascend in a balloon on October 15, 1783, was a physician-apothecary from Metz, Jean Pilatre de Rozier (1756–1785). He subsequently became the first martyr to aeronautics when he perished in an attempt to emulate a Boston physician named Jeffries, and Pierre Blanchard, the first two men to cross the English Channel in a balloon. And it was Paul Bert, a pupil of Claude Bernard, who founded aeronautical medicine, today a vital part of modern medicine and the key to tomorrow's interplanetary navigation.

What was the moving spirit of these physician-explorers? Men who aspire to rise above their mortal destiny by perpetuating their lives through history are always impelled by two great instinctive motivations: the yearning for truth and the love of power. Truth is sought along the broad paths of science, beauty, or religion. Power must be pursued through the devious channels of money, politics and war.

But the explorer's soul is different. He desires something loftier though less useful than authentic science, vaguer but less selfish than possession. Perhaps the most genuine way of satisfying an instinct is through the instinct itself. To suffer in order to know, and to know in order to know. That is, to seize the torch of knowledge—*cursu lampada trado*, as Lucretius said—and transmit it ablaze to posterity.* That is the clue to the work of the great traveling doctors.

With such precursors it is not surprising that physicians are showing more and more interest in protecting their patients against stress and other dangers of travel.

This Symposium will attempt to present a panorama of medicine's contribution to the protection of the traveler's health today, whether the traveler is a man, woman, or child, old or young, healthy or sick, on land, on sea, and in the air, in tropical or polar zones, in great bustling cities or lonely silent deserts, thus crystallizing the dream of making good health as inseparable a companion of the traveler as his passport.

In reality, the objective of medicine as applied to travel is to practice that basic philosophical principle recommended by Claude Bernard as the supreme objective of all vital mechanisms: ". . . to preserve intact the living conditions of the inner milieu . . ." regardless of the means of locomotion used or the new environment to which the traveler is transported.

Let us end by remembering, as a symbol of this Symposium, that in Greek mythology Delphi held the center or *omphalos* (navel) of the orb, because, according to the legend, if two eagles soared into the air from the two ends of the earth they would inevitably meet in Delphi. The two eagles of modern Preventive Medicine and Scientific Research are today soaring towards a point situated not in Space but in Time. The temple to which their wings will carry them is located in the future.

* Doctor G. Marañón, of Madrid, has made a fascinating study of the philosophy of explorers in his essay "El Príncipe explorador" (Meditaciones, G. Marañón, Cultura, Santiago de Chile, 1937).

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When Children Travel

Wordsworth said that "the child is the father of the man." Children in the past traveled under most dangerous conditions; in some cases, as in the Children's Crusade in 1212 A.D., they were exposed to infections, traumatisms, and insufficient food. Mercifully, times have changed. What Medicine can do today "When Children Travel" will be presented now by a renowned pediatrician, author and gentleman-traveler, Dr. I. Newton Kugelmass.

Positive Effects of Traveling with Children. Three vectorial requisites must be fulfilled in traveling with children—effective start, worthy goal, and spaced itinerary. Children are always at home in motion when they travel in the company of those they love, hence preliminary arrangements should provide youngsters with their accustomed though abbreviated routine. The proposed trip should be announced days not weeks ahead to avoid anticipation, excitement, and jubilation. The prelude to travel requires several days of daily routine that simulates the conditions of actual travel for gradual adaptation to continuous change en route. Once the decision is made the trip should start as planned. Parental puttering weighs heavily on youngsters. A worthy goal in traveling gives children a sense of power to achieve that which is beyond their grasp. New reserve powers are tapped when they respond to new situations en route. Children develop organic power to endure, neuromuscular power to respond quickly, mental power to solve problems, emotional power to feel new sensations. A spaced itinerary commensurate with the child's bodily capacity for travel affords maximum enjoyment with minimum fatigue for all the trouble.

Effective traveling transforms a child spectator into a participant. Modern life is characterized by the great mobility which comes from convenient modes of transpor-

Presented at The First International Symposium on Health and Travel on June 23, 1955, in New York City.

tation. Normal children enjoy the freedom from limitations of space and time, the novelty of new experiences and environments, the stimulation of diverse adjustments in traveling. Such activities and interests provide opportunities for active participation, creative effort, relations that can be shared or felt by others, and for personality enhancement. Such interests are preferable to spectator interests which are brief, solitary, noncreative, or even destructive of the personality.

Traveling creates a child problem-solver out of a daydreamer. The solution of everyday problems is a direct outcome of the child's efforts to use his own resources in the way of bodily equipment, training, and experience. It involves many kinds of thinking—daydreaming at one extreme, imagination beyond that extreme and problem-solving at the other extreme. Traveling bans daydreaming and regulates imagination by realism. The child sees things as they are instead of thinking how they may be. Traveling is an excellent form of training in projects and problems rather than in information alone. It keeps the child in a real world and enables him to experience the satisfactions which come with meeting and solving new problems.

Disturbing Oscillations in Motion Sickness of Children

Continuous movement, uniform velocity, one direction → no motion sickness
Motion, speed or direction varied repeatedly → acceleration sickness

Linear accelerations (elevator, train, plane) → Saccular macula
Angular accelerations (swing, auto, ship, plane) → cristae semicircular canals

Up and down ↑↓ > Fore and aft ⇄ > side to side ⇄
Rectilinear (car, train) > Rotatory (air, sea)

Determinants of Motion Sickness in Children

Oscillating Media	Predisposing Factors	Exciting Causes	Clinical Manifestations	Immunity
Animal	Malventilation	Labyrinthine	Pallor	Infants,
Hammock	Olfactory stimuli	Eyestrain	Nausea	pre-walking
Swing	Visual impressions	Muscle sense	Vomiting	Deaf mutes
Elevator	Hypoxia	disturbance	Vertigo	Children with
Car	Fatigue	Peripheral nerve	Colic	spinning
Train	Noise	stimulation	Lassitude	practice
Ship	Indigestion	Psychic stimuli	Depression	Vestibular
Plane	Discomfort	Illness	Blurred vision	apparatus
Merry-go-round	Overindulgence	Sudden motion	Cold sweating	destroyed
	Psychic stimuli		Headache	Ablation
	Emotional instability		Ketosis	chemoreceptor
				trigger zone

Traveling teaches adjustment to life's stresses and strains. The child learns to face real situations, to distinguish between the significant and insignificant, to work out his own way of life in the midst of new pressures. He learns to attack problems

en route in a straightforward yet flexible way without bowing under every wind that blows, or getting alarmed at meeting difficult situations. Adjustment is gradually revealed as he moves from one circumstance to another without necessarily showing old emotional responses in new situations.

Traveling develops self-reliance. It is specific for each new situation rather than a general tract for all situations. It gives a child various opportunities for practice and responsibility appropriate to his age and ability, tempered by parental guidance in making his own decisions. The spirit of self help becomes the source of growth in the child. Help from without is enfeebling while help from within invigorating. Traveling develops self-reliance in all its aspects in an atmosphere of mutual confidence, affection and companionability.

Mechanism of Motion Sickness. Motion sickness occurs in 80 per cent of traveling children. The designation of the disease is a misnomer since continuous movement at uniform velocity in one direction does not induce nausea. When the speed or direction of motion is repeatedly varied children develop acceleration sickness, an abnormal sensitivity to one or more types of motion. A child may be susceptible to only one type of motion but more often the same child is abnormally affected by any type of severe motion. It is due to failure of physiologic adaptation in individuals exposed to frequently repeated changes in the velocity of elevators, hammocks, swings, amusement devices, animals, cars, trains, ships and planes. Linear accelerations developing in elevators, trains and planes stimulate saccular macula while angular accelerations in swings, merry-go-rounds, autos, ships, and planes stimulate the cristae semicircular canals. Up and down movements disturb children most, side to side movements least, and fore and aft moderately. Rectilinear motion in cars and trains upset children more than rototary movements in planes and ships.

Motion sickness is a useless reaction, a relic of some ancient purposeful response. It is probably due to a particular pattern of vestibular discharges generated chiefly in the uticles of the labyrinth and stimulating pathways through the cerebellum to the brain stem. A lengthy process of summation of such discharges is required before the effect is achieved. The process is favored by visual, visceral, and psychic influences, reduced by the supine position and totally absent in children accustomed to spinning, in those where vestibular apparatus is destroyed, and in deaf mutes.

Predisposing causes of motion sickness are poor ventilation, pungent odors, ex-

Children's Responses to Abnormal Movement or Varied Acceleration

Manifestations	Children Sympatheticotonic: (Excitation)	Adolescents Vagotonic: (Inhibition)
Nausea	Frequent	Infrequent
Vomiting	Marked	Mild
Headache	Late or absent	Early and persistent
Vertigo	Late	Early
Pulse rate	High	Low
Blood pressure	High	Low
Drugs	Sedatives	Alkaloids

cessive fatigue, the sight of vomiting, psychic impressions, visual fatigue, dietary indiscretion, shrill noise, extreme cold, emotional instability, and physical illness. Physiologic factors predispose to motion sickness whether the anxiety arises from the environment producing the motion or from the knowledge that onset of symptoms is inevitable as evidenced by definite protection afforded by a placebo in a large proportion of suggestible children.

Exciting causes are sudden onset of motion, stopping and starting of a car, tremor and vibration of a motor, irregular bounce of a plane, rapid rise and fall of an elevator, or circular motion of a merry-go-round. Rectilineal movements of a car or train produce greater motion sickness than rotating movements of a plane or ship. Up and down oscillations are more disturbing than fore and aft or side to side movements. The resulting disturbance in equilibrium causes a splanchic fatigue from bombardment of afferent impulses on the secondary nerve centers. The stimuli escape from the reflex and subcortical control with a resulting series of symptoms from the medullary center.

Labyrinth overstimulation causes an overflow to the vagus, respiratory and other centers with consequent vomiting, dizziness, irregular breathing, and sweating. The greater the sensitivity of the labyrinth, the earlier and more intense the symptoms. Preschool children are particularly liable to motion sickness from mild excitation of a car or train but infants devoid of orientation show no such symptoms. Eye strain produces digestive symptoms with headache. Yet, blind children suffer from seasickness. Ocular muscle imbalance in children with insensitive labyrinth may precipitate motion sickness.

Peripheral nerve stimulation is a determining factor in childhood motion sickness. The interplay of tension and pressure in the abdominal cavity affects the nervous mechanism. The action of the vagus dilates the cardia and increases the action of the pylorus with consequent tension on the large nerve plexus of the sympathetic system. A child susceptible to motion sickness will be relatively free in the prone position unless disturbed by psychic stimuli difficult to control, especially in the emotionally disturbed and unstable child.

The stable child with a healthy personality responds to prophylaxis and resists motion sickness. But the unstable child charged with mistrust, doubt, guilt, inferiority, diffusion, isolation, self-absorption, and despair shows a preponderance of unfavorable innate disabilities. Such an unhealthy personality is most susceptible to motion sickness. Indeed, 15 per cent of the children who resist prophylactic measures and succumb to motion sickness reveal abnormal personality traits. The inherent difficulty in overcoming the psychic aspects of motion sickness is vested in deep-seated personality problems of the growing child.

Manifestations of Motion Sickness. The signs and symptoms depend on the susceptibility of the child and the intensities of the oscillations. Heredity is a determining factor but the emotional climate is more decisive. An active youngster suddenly becomes quiet, begins to yawn, shows apathy, senses internal changes, wants to be left alone and refuses food and play. Susceptibility predominates in the linear build with nervous temperament, apprehensive attitude and cold extremities. The mild case in car and train sickness reveals giddiness, drowsiness, gastric distress bordering

on nausea but rarely headache. The moderate or severe case in air or sea sickness shows anorexia, nausea with or without vomiting, persistent vertigo, unsteady gait, facial pallor, cold extremities, marked weakness, and mental apathy.

The degree of disturbance depends upon the predominance of excitation or inhibition in the affected child, the one occurs in younger children of the sympatheticotonic type, while the other in adolescents of the vagotonic type. The excitable young child of the sympatheticotonic type develops nausea, vomits, has dizziness but no headache despite high pulse rate and high blood pressure, and requires long-acting sedation and antihistaminics. The inhibited adolescent of the vagotonic type develops little nausea or vomiting but persistent headache and dizziness with low pulse rate and low blood pressure and requires alkaloids and antihistaminics. Hill (1939) found that most cases belong to both types because early vagotonia gives way to sympatheticotonia with fatigue. Not all illness en route necessarily connotes motion sickness. Differential diagnosis includes intestinal indigestion, appendicitis, intesusception, obstruction, or onset of an acute infectious disease.

Prophylactic Procedures During Traveling. Feeding regulation of an infant while traveling for a day or two requires preliminary refrigeration of the formula. The bottles can be carried in insulated bags, thermos bottles, dry ice containers, or refrigerated in the traveling vehicle. Traveling for weeks or months requires preliminary adjustment of an evaporated or dry milk formula to the infant several days before the trip. Essential materials consist of 5 oz. cans of evaporated milk, pound containers of dextrimaltose or Karo, a day's supply of sterilized nipples and bottles, a quart of sterilized water as well as a funnel, spoon, brush, can opener, and electric bottle warmer. An infant cannot adjust to changing sources of drinking water. A large thermos bottle of the accustomed water should be taken along or bottled spring water obtained en route and the same source of water offered throughout the voyage. Water is an unsuspected medium of contamination with organisms inducing intestinal infection.

Each feeding can be prepared separately or preferably all feedings for 24 hours with refrigeration facilities. It merely involves introducing the correct volume of sterile water into the bottle, dissolving the sugar, adding the evaporated milk, shaking and heating in the electric warmer or under a hot water faucet. After the feeding, the bottles, nipples, funnel, can opener, and spoon are washed, drained, and dried.

The infant formula is usually supplemented by a variety of solid foods at mealtime. Foods to which the baby is already accustomed should be taken along in strained form in cans. The foods selected for each meal should be warmed before opening and fed directly from the tin. An infant will not take as much food en route as at home, hence forcing is psychologically wrong. It is more advantageous for a baby to consume a balanced feeding and digest it well than to exceed his tolerance and succumb to indigestion.

An infant's daily routine en route should approximate that at home. Abrupt changes in established habit patterns induce fretfulness and irritability. The baby should be rested before and put to sleep immediately after feedings and play between feedings alone or with traveling companions. Bowel control, if established is favored by such an accustomed routine. Constipation tends to affect the sedentary

child unaccustomed to travel. It is preferable to take some form of prune product—juice, mash, or dried prunes—to induce a normal movement rather than to rely on laxatives en route. A disposable diaper is most desirable. If a stool is not forthcoming with the change in regimen, there is no need for laxative procedures during a 48 hour period.

An infant should be dressed according to the temperature of the compartment or stateroom during traveling and according to the temperature of the destination before the end of the journey. All raiment should be light in weight and readily laundered, allowing two or more changes than the actual number of days traveled. A pillow, blanket, rubber sheet, and a supply of pads are invaluable for the infant's bed accommodations. A folding toilet seat should replace the public toilet seat.

Prophylactic Procedures in Traveling with Children

Infant Foods:	Milk, evaporated or dried; sugar, sterile water, canned cereals, fruits, vegetables and fruit juices.
Formula Materials:	Bottle warmer, formula and thermos bottles, nipples, funnel, spoon, brush, can opener, toilet seat.
Diet Therapy:	High alkaline-forming foods, high carbohydrate, high salt, low fat, low fluid; avoid overindulgence and offending foods; avoid cold eggs, prepared salads, stale sandwiches, cold meats, cold fish, mayonnaise, milk puddings, pastries with moist fillings.
Play Therapy:	Dolls in minature cars, trains, planes, favorite cuddly toys, coloring and cut-out books, open-air exercise between meals, avoid eyestrain, encourage dark glasses.
Antihistamines:	Bonamine, Dramamine, Marezine, Lergigan, Perazil 12.5 mg. t.i.d. in moderate, to 50 mg. in severe turbulence.
Alkaloids:	Hyoscine gr. 1/500, Hyoscyamine gr. 1/250, Amphetamine mgm. V t.i.d./ac, combined with antihistamine.

An older child's diet should be alkaline-forming to improve acid-base balance, high in carbohydrate to prevent ketosis, high in salt to maintain hydration, low in fat to accelerate digestion, low in fluids to avoid gastric distention. Food obtained in public places should be simple, easily digestible, and boiled. Essential foods are universally available in palatable form. It is a great mistake to exceed the holiday spirit with new types of food or unaccustomed preparations. An apparent treat may cause needless difficulty. The author (1948) advises parents not to offer cold eggs, prepared salads, stale sandwiches, cold meats, cold fish, milk puddings, cakes and pastries with moist fillings, all of which are easily contaminated with poisonous bacteria if carelessly handled or improperly refrigerated. A traveling child should be given hot, freshly prepared foods, fresh milk in separate containers, and water from a thermos bottle to prevent digestive illness en route.

Play therapy releases tension especially in the emotionally disturbed or unstable child. Conn (1939) showed that a child releases negative feelings by playing with dolls in miniature cars, trains, and planes. It transforms negative into positive atti-

tudes towards travel. The traveling child should have his favorite cuddly toys for bedtime companionship and the older child color forms and cut-outs for daytime preoccupation. Open air exercise should be provided between meals without inducing fatigue. Rest should supersede all activities after meals. The child should be kept from stuffy lounges or smoking rooms. Eye strain should be avoided by eliminating staring at the glistening ocean or passing trains. Closure of the eyes and wearing colored glasses diminishes eye tension. When the ship is pitching the child should lie athwart the vessel; when it is rolling he should lie fore-and-aft.

Drug therapy includes sympathomemetics, antihistaminics, sedatives, and alkaloids in individualized combinations given before starting the trip. All are central nervous system depressants and produce drowsiness. Whether their effectiveness is due solely to such general action or whether some drugs have a specific action on the vestibular apparatus is not settled. The sympathomimetics, amphetamine, and dextroamphetamine, influence child behavior favorably during travel largely by altering the emotional reaction to disturbing situations. The antihistaminics, dimenhydrinate, diphenhydramine, dramamine, benadryl, lergigan, bonamine, merazine, and others are effective in motion sickness by depressing vestibular function. Congeneric compounds may eventually prove superior. But their mode of action is unrelated to antihistaminic action or sedation. A teaspoon of dramamine contains 12.5 mg., an adequate dose for a five-year-old. The appropriate antihistaminic is administered prophylactically in moderate to full dosage 30 to 60 minutes before exposure to motion. The dose is repeated before meals and upon retiring or increased for the duration of the exposure, depending upon the degree of turbulence. The effectiveness of the drug is diminished after signs and symptoms have developed. Antihistaminics are less effective in air-sickness than in other forms of motion sickness in children. All tend to have unfavorable side effects such as tinnitus, blurred vision, drowsiness, and mouth dryness.

Therapeutic Procedures in Severe Motion Sickness

Psychotherapy:	Combat fear, apply autosuggestion, act reassuringly, avoid offensive odors, guard against nauseating stimuli, isolate from seasick persons, distract with pleasant tales, divert from self-preoccupation.
Labyrinthine:	Eyes kept closed, head in a steady fixed position, head flat in horizontal position, head backward in sitting position, cold towel to forehead, prevent side-to-side head motion with pillow.
Nutrition:	Eliminate solid food first few hours; small, bland, frequent meals; high carbohydrate, high salt, low fat, low fluid; avoid individually offending foods; crackers, coca-cola, lollypops between meals; acidosis combated by rectal retention: dextrose 1 tablespoon, water 4 oz. q. 4 h., containing required drugs.
Vagotonia: (Adolescents)	Atropin gr. 1/240 or belladonna Mx or hyoscine gr. 1/200—caffeine gr. 1 or strychnine gr. 1/120 (for depression).
Sympatheticotonia: (Children)	Chlorbutanol gr. V; Choral gr. XV; Bromide gr. V; Sodium amytal gr. I; Phenobarbital gr. I.

Types of Dehydration

Manifestations	Salt Depletion	Water Deficiency
Clinical features		
Thirst	Not remarkable	Intense
Skin turgor	Decreased	Normal
Pulse	Rapid	Normal
Blood pressure	Low	Normal
Laboratory findings		
Serum proteins	Increased	Normal
Hemoglobin and hematocrit	Increased	Normal
Nonprotein nitrogen	Elevated	High normal
Plasma sodium and chloride	Reduced	Elevated
Urine volume	Not remarkable	300–500 cc/day
Urine concentration	Not remarkable	Maximal
Treatment	Salt	Water

The belladonna alkaloids, scopolamine, or hyoscine and related compounds act centrally in the prevention and alleviation of motion sickness. Chinn (1953) finds these compounds more effective prophylactically, in combination with an appropriate antihistaminic. Scopolamine gr. 1/500 with diphenylhydramine mg. 15 is particularly effective. Amphetamine and barbiturate do not enhance the potency of such combinations. A small dosage of scopolamine eliminates the alarming side effects of blurred vision, headache, dry mouth, and fatigue.

Therapeutic Procedures in Motion Sickness. A mild attack of car or train sickness may be combated by keeping the head in a steady fixed position, flat in the horizontal position, or backward in the sitting position, always exposed to fresh air. The pillow should be adjusted to reduce to a minimum any side-to-side motion of the head. The child's eyes should be kept closed. The individualized antihistaminic or particular combination of prophylactic drugs should be continued three times daily and at bedtime. Fluids should be restricted for the first few hours but later small sips of fluids can be given at frequent intervals, gradually replaced by fresh fruit juices or tea and supplemented by lollypops or hard candies to maintain blood sugar and hydration. Solid foods are contraindicated.

A severe attack usually affects older children but they have a remarkable capacity for rapid recovery. The psychic factor is most difficult to manage. The child should be put into the recumbent position for minimal stimulation of the labyrinthine, reassured to gain mastery of his instability and encouraged to play for diversion from self-preoccupation. The child should find a position most favorable for equilibrium and persist with reassurance until able to change that position without ill effects. Sometimes, a tight abdominal binder will prevent abnormal intestinal motion, force the blood from the abdomen into the systemic circulation, and help combat motion sickness.

Feedings should theoretically be optimal because a hearty meal induces drowsiness and a full intestine thwarts pull and pressure changes. Practically, small bites of

crackers more or less continuously, alternated with sips of cold coca cola are well tolerated until small meals can be resumed. Partial starvation tends to induce an acidosis which aggravates the vomiting. Two types of dehydration acidosis must be differentiated for effective treatment, the one involves water depletion and the other salt depletion. Water deficiency is manifested by intense thirst, normal skin turgor, pulse rate, blood pressure and serum protein, but elevated nonprotein nitrogen, plasma sodium and chloride and concentrated urine. Salt depletion on the other hand shows no thirst but decreased skin turgor, rapid pulse rate, low blood pressure, high serum protein, high nonprotein nitrogen and low plasma sodium and chloride. Treatment for water deficiency requires water and dextrose, while treatment for salt depletion requires physiologic saline in water by rectal retention at three to four hour intervals or parenterally if possible en route.

Alkaloids are effective in children of the vagotonic type. Tincture of belladonna 10 to 20 minims at four hour intervals or 1 to 2 minims of 1 per cent atropine sulfate will allay vomiting and combat vagotonia. The vagus may be stimulated by epinephrine 1/8 gr., prophylactically, by strychnine therapeutically and by caffeine as a grain of citrate or as strong coffee. Some prefer a combination of strychnine gr. 1/120 and atropine 1/240 parenterally until dryness of the mouth is induced. Others prefer scopolamine gr. 1/100 in small repeated doses to prevent reactions and produce a sustained effect, adding strychnine gr. 1/120 to combat depression.

Sedatives are particularly effective in children of the sympatheticotonic type. An older child may be given chlorbutanol capsules gr. 1, q. 4 h. to prevent vomiting and calm the child. A combination of bromides and chloral hydrate may be given orally in the dose prescribed above and rectally twice that dose until sleep is induced. The longer acting barbiturates are preferable to the shorter acting compounds although their cumulative effects are detrimental in acidosis. Protracted vomiting may be arrested by morphine gr. 1/24 and atropin 1/240 hypodermically and the head not raised for several hours. Upon arising, the child should be given cracked ice, strong coffee, or iced coca cola. If vomiting recurs one-half the previous dose should be continued q. 4 h.

Residual post-motion sickness may be alleviated immediately upon arrival by offering oxygen inhalation for 10 minutes, a full meal, amphetamine mg. V t.i.d. and vitamin B-Complex for 24 hours.

Febrile Illness During Traveling. Healthy children may develop a rectal temperature up to 101 F. after prevoyage excitement, children's parties, or strenuous day due to increased heat production in the surrounding pelvic musculature. Fever may also be due to excessive exposure to heat or to excessive clothing in hot weather. Children normally show a diurnal variation in temperature amounting to as much as 2 degrees with the peak in the late afternoon and the low point during sleep. But fever is usually the initial symptom in different types of disease, especially infection, dehydration, or central nervous system disease. A child's temperature rises more readily than an adult's, hence a high fever does not have the same significance at every age.

Fever often has a beneficial effect in combating infection. Indeed, failure to develop fever in the presence of severe infection signifies a grave prognosis. On the

other hand, the actual presence of fever has little bearing on the outcome of ordinary infections. The fever that accompanies noninfectious conditions serves no useful purpose. Moderate fever of several days duration is not harmful and should not excite parental anxiety. But high fever should be reduced to prevent irritability, restlessness, and sleeplessness. The presence or absence of these symptoms is more of a guide than the degree of the temperature in determining whether or not to interfere with treatment en route.

Hydrotherapy is the most satisfactory method for combating fever. It involves a sponge bath of equal parts of alcohol and water at hourly intervals. Colon irrigation is another method of reducing fever and eliminating intestinal accumulations from persistent constipation so prevalent during traveling. Drugs should be offered only if necessary in the accustomed form and dosage which the child tolerates best. Aspirin, 2½ gr., at 4 hour intervals for simple fever; an antibiotic such as tetracycline, 100 mg. every 4 hours for infectious fever; sulfasuxidine gr. IV q. 4 h. for fever accompanied by diarrhea; ¼ per cent neosynephrin nose drops for relieving nasal obstruction. These medicaments should be included when traveling because they cannot be obtained without prescription. If the febrile illness persists despite treatment with available medicaments, a doctor should be consulted en route or in the first community reached or the child taken to the nearest hospital in that town for diagnosis and treatment.

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When People Who Are Not Young Travel

Throughout history old people have always been active travelers. In the Renaissance, sailors and soldiers were chosen first from among old people, who had through the years accumulated vast reserves of stamina as well as great world experience. The ever rising number of old people in most parts of the world makes it imperative that physicians protect these aged people from travel stress. A distinguished teacher, clinician, and author, Dr. William T. Foley, will now talk to us about "When Old People Travel."

The medical problems of travel are bacterial, psychologic, climatic, and postural. Older people have a great advantage in the first two categories, less so in the latter two.

The traveler finds himself in a new world of microscopic organisms. Wendell Wilkie was wrong—it is not one world, and Thomas Jefferson was wrong—we are not created equal from the point of view of a bacterium.

To most bacteria, protozoa and viruses, we humans have developed a racial immunity. When these living organisms are able to break down our defenses against them, then we develop disease. This immunity, however, varies among different races. Once I had occasion to care for a large group of men in a war prison camp. Chicken pox broke out amongst us. The white races had only a mild illness, but the Polynesian boys, also prisoners, had severe sickness and several lost their lives.

Many of you will remember H. G. Wells' story of the invasion from Mars. These inhabitants from our nearby planet landed in force and conquered everything in their path. In several days, however, they were all dead—of the common cold. If there

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are any among us who plan trips to other planets, I suggest preparations against the local bacteria there. Seriously, I think we have fairly good evidence of vegetative growth on Mars. All vegetable life depends on microorganisms. So be sure to make your space suits impenetrable to bacteria.

A traveler soon finds that although his gastrointestinal tract is immune to all local bacteria, foreign cities have organisms to which the local population are immune, but to which he is not. From 1938 to 1941 I was stationed as a medical officer in various cities in China. Each city had its own type of diarrhea—Swatow belly, Amoy belly, Shang Hai belly, Hong Kong belly. These were the less profane terms used to describe these ailments. They simply represent the squabble that goes on every time a new group of bacteria take up light housekeeping in the colon. Until they compromise with their host and landlord, life is not very pleasant.

How can the traveler protect himself? Once I aided the Red Cross in dealing with a cholera epidemic in South China. The disease was widespread. People were literally dying by the hundreds in the streets of Canton and surrounding villages.

My work took me to native towns where there were no foreigners and only native inns to stop at. One slip and I myself would have cholera. In ordering meals I first sent for a bowl of boiling water. In China one can get anything for money, even such an outlandish thing as that. In this steaming water were placed my chopsticks and rice bowl for five minutes. Then the food was brought in steaming hot. I never took ill from an intestinal ailment during seven years in the Orient—1938 to 1945—and on numerous trips in Europe and South America since then. In China, of course, no one drinks water, only hot tea. While traveling, if one eats only hot foods, the new bacterial invaders of the intestinal tract will be warded off.

Victor Heiser, who directed the Rockefeller Foundation work in the Orient for many years, tells the story of a cholera outbreak in Manila and the nearby barrios. His trained native helpers were quickly dispatched to teach the people to drink only water that had been boiled. One barrio persisted in having cholera so Heiser himself went to inspect. He went from house to house. Sure enough all the inhabitants drank boiled water. Finally he asked one of them, "How much do you drink?" and received the amazing answer, "One teaspoonful three times a day."

Recently we were accused by the Chinese of waging bacterial warfare in Korea. Dr. Crawford F. Sams, the medical corps general of MacArthur's staff, has shown that this accusation was made simply to cover up the inability of the North Koreans to cope with epidemics of smallpox, typhoid, and typhus which reduced their population from 10,000,000 down to 2,000,000 during the war.

But in view of the Chinese accusation, I would like to tell my story of the impossibility of waging germ warfare in China.

In the spring of 1939, I was the medical officer of the *U. S. S. Asheville*, an ocean going gunboat. We had been in several outports, not designed for the enjoyment of sailors, and then put in at Hong Kong, which is. One of the men met with more than he had bargained for in a Hong Kong house of joy. After we put out to sea he came down with typhus fever. Our next port was Chinwangtao, the northernmost port in China proper—near where the Great Wall goes into the sea. In 1938, I had only been a Navy physician for two years, and was very much impressed by the

rules in the book. Typhus is one of the seven quarantinable diseases the world over. Any ship that has had a case on board, when coming into a port, must fly the yellow flag and anchor in a designated spot and await inspection by the port health authorities.

I duly informed the ship's captain of these regulations. We came into port early one morning and dropped the hook. We waited. One hour went by. We waited and waited. Finally at noon, a very distraught and irritable captain sent for me and ordered me ashore in a boat to hunt up the health authorities. Although this was strictly against regulations which specified that the ship must have no contact with the shore, I obeyed. On reaching the quai side I inquired for the doctor and was told to look in the club. Every port in China had a customs club, thanks to British culture. On entering the club I was told to look in the bar for the doctor. I found him, introduced myself, and then very apologetically informed him that we had had a case of the dreaded typhus fever on board. He looked me up and down, frowned and said, "By any chance do you think you could bring us any disease up here?" I was soon to find that North China has every epidemic disease in the text book.

PSYCHOLOGIC FACTORS

The ability to adjust to stress comes with experience. In this sphere, age has an advantage over youth. To illustrate this I would like to allude once again to the prison camp. I had been serving as medical officer of the U. S. Marine Corps Detachment of Tientsin, China. On our way to Corregidor, at the outbreak of the war, we ended up as prisoners. Also in this camp were the remnants of our forces on Guam, Wake, the survivors of ship sinkings, and plane crashes. In all, we totalled about 1500 officers and men.

We were imprisoned for nearly four years. During this time we were shifted to Central China, North China, Manchuria, Korea, and finally to the mines in Japan proper. Every type of disease and psychologic stress was encountered. It was the young who had the most difficulty and who succumbed. The older men were able to take things in stride and adjust quickly to each new adventure.

CLIMATIC ADJUSTMENTS

Time does not permit a detailed discussion of temperature and altitude variables and their effect on personnel of different age groups. Again, the ability to adjust is the deciding factor.

During our stay as guests of the Japanese Emperor, we spent four winters with no heat and insufficient clothing, in regions of intense cold. At one time our camp was located at a mining site at such a high elevation that water boiled at a low temperature, too low to cook the small amount of rice we had to eat. The only cases of frostbite were among the young and foolhardy. The older men knew how to protect themselves.

POSTURE

A large part of my work these days is in the fields of circulation. Travel, which

requires sitting for many hours in a plane, train, or car, is very taxing on the venous and lymphatic flow. Many people experience varying degrees of swelling of the feet and ankles after a long trip. The maintenance of good circulation requires body motion. Wearing constricting garments of any kind gives a tourniquet action against the flow of body fluids from the extremities.

This part of my paper is aimed especially at the ladies. The girdles they wear, according to the advertisements, are wonderful for jumping through hoops, posing on one foot, or pushing balloons up to the ceiling. They are designed for women standing up—but not for sitting.

In closing, I would like to thank you for listening and summarize my advice as follows: When you travel, eat hot food, drink tea or boiled water, get up and walk around every hour, and leave your girdles at home.

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Infections and Travel

Infections have been the most universal of all scourges of mankind, and throughout time and space the greatest cause of death in History. Medicine today counts on powerful new weapons to fight infection, to prevent it, and to treat it. Doctor Elmer Loughlin, a distinguished clinical investigator and author, who is also a well seasoned traveler, will now discuss "Infections and Travel."

The enjoyment of travel to distant lands, including even those of the tropics, need not be marred by sickness due to infections then or later. The infectious diseases or fevers of tropical regions are no longer mysterious; they are generally preventable and in most instances respond readily to modern treatment. The establishment of health programs in many tropical countries with improved sanitation and living conditions for native people, mass immunizations, control of certain contagious diseases with antibiotics, and control of vectors of certain human and animal infections by the mass application of insecticides, have contributed to making travel to these countries reasonably safe and to opening underdeveloped lands that only a decade ago were considered perilous.

The common infectious diseases of western Europe, whether they occur in London, Paris, Madrid, Rome, or Vienna are much the same as those in New York, Chicago, San Francisco, or Montreal. Respiratory infections, for instance, whether in Europe or the United States, are quite similar and the average American physician is fully competent to treat them as well as to give expert advice on their prevention or prophylaxis. The average physician is intimately acquainted with the common contagions of childhood, their prevention by immunization, periods of incubation, prodromal symptoms, isolation requirements, and their treatment, or that of their complications, with modern chemotherapy or antibiotics.

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On the other hand, the infectious diseases of the tropics (*sensu latu*) have topical as well as seasonal dissimilarities. Modern travel has put a girdle around the earth and has so reduced distances figuratively between temperate and tropical zones, that a knowledge of infectious diseases of the tropics can no longer be considered as the restricted province of the specialist in tropical medicine.

Since Americans generally are health conscious, it is improbable that any would become panicky or that more than a few would be deterred from traveling if they were apprised of the infections that might be encountered along their proposed itinerary and provided with practical information about how they can be avoided by proper immunizations and by exercising comparatively simple precautions en route as well as at their destinations. Although some of this information can be procured from Public Health Service headquarters or clinics and from foreign consulates, the average prospective traveler usually finds it quite complicated to obtain simple instructions concerning required immunizations. Also, his personal physician seldom has attained sufficient geographic versatility to furnish adequate information about infectious diseases en route and the precautions that should be observed to avoid acquiring them. It would not seem presumptuous, therefore, that the prospective carrier should provide the traveler's personal physician with information concerning infections along the proposed itinerary, and for his future reference: pertinent data on the traveled parts of the tropical world (*sensu latu*), information on indigenous infectious diseases, their epidemiology, periods of latency, precautionary measures, immunizations, prophylactic and suppressive drugs, and recommended anti-infective therapy with chemotherapeutic and antibiotic agents, as well as those medications that will be useful for the symptomatic relief of incidental disorders.

IMMUNIZATIONS AGAINST INFECTIONS

According to international covenant, certain immunizations are required to avoid delay or detention in quarantine en route or upon return to a port or border station of the United States. Since most governments also require an International Certificate of Vaccination, properly certified by authorized physicians in their country of origin, this certificate should be procured early, preferably at the time arrangements for traveling are being made. This certificate of vaccination should be carefully kept with the passport or other documents of travel. Immunizations should be renewed as often as required for international travel as well as for optimal protection against infection.

Most persons recognize that certain immunizations are required to protect them against corresponding contagious diseases, yet it is not unusual to encounter an adult who may not have been vaccinated since early childhood. In their well-sanitated home environments most adults fortunately are seldom exposed to infections that might be prevalent in the tropics and they do not acquire these diseases against which they should be immunized. It is considerably different when they travel to tropical lands where exposure is far more likely. In order to avoid acquiring some infectious diseases while traveling in the tropics it is requisite that the traveler be immunized against them. The traveler should be impressed with the fact, how-

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Presented at The First International Symposium on Health and Travel on June 23, 1955, in New York City

On the other hand, the infectious diseases of the tropics (*sensu latu*) have topical as well as seasonal dissimilarities. Modern travel has put a girdle around the earth and has so reduced distances figuratively between temperate and tropical zones, that a knowledge of infectious diseases of the tropics can no longer be considered as the restricted province of the specialist in tropical medicine.

Since Americans generally are health conscious, it is improbable that any would become panicky or that more than a few would be deterred from traveling if they were apprised of the infections that might be encountered along their proposed itinerary and provided with practical information about how they can be avoided by proper immunizations and by exercising comparatively simple precautions en route as well as at their destinations. Although some of this information can be procured from Public Health Service headquarters or clinics and from foreign consulates, the average prospective traveler usually finds it quite complicated to obtain simple instructions concerning required immunizations. Also, his personal physician seldom has attained sufficient geographic versatility to furnish adequate information about infectious diseases en route and the precautions that should be observed to avoid acquiring them. It would not seem presumptuous, therefore, that the prospective carrier should provide the traveler's personal physician with information concerning infections along the proposed itinerary, and for his future reference: pertinent data on the traveled parts of the tropical world (*sensu latu*), information on indigenous infectious diseases, their epidemiology, periods of latency, precautionary measures, immunizations, prophylactic and suppressive drugs, and recommended anti-infective therapy with chemotherapeutic and antibiotic agents, as well as those medications that will be useful for the symptomatic relief of incidental disorders.

IMMUNIZATIONS AGAINST INFECTIONS

According to international covenant, certain immunizations are required to avoid delay or detention in quarantine en route or upon return to a port or border station of the United States. Since most governments also require an International Certificate of Vaccination, properly certified by authorized physicians in their country of origin, this certificate should be procured early, preferably at the time arrangements for traveling are being made. This certificate of vaccination should be carefully kept with the passport or other documents of travel. Immunizations should be renewed as often as required for international travel as well as for optimal protection against infection.

Most persons recognize that certain immunizations are required to protect them against corresponding contagious diseases, yet it is not unusual to encounter an adult who may not have been vaccinated since early childhood. In their well-sanitated home environments most adults fortunately are seldom exposed to infections that might be prevalent in the tropics and they do not acquire these diseases against which they should be immunized. It is considerably different when they travel to tropical lands where exposure is far more likely. In order to avoid acquiring some infectious diseases while traveling in the tropics it is requisite that the traveler be immunized against them. The traveler should be impressed with the fact, how-

ever, that he must not be so naive as to assume that the immunity resulting from vaccination will provide absolute protection, or that it can be considered as a substitute for heeding hygienic precautions.

Everyone traveling to tropical lands must be recently vaccinated against smallpox and should be immunized against typhoid and paratyphoid fevers, as well as against tetanus. Although diphtheria is not considered to be a tropical disease, it is, nevertheless, endemic in many regions of the tropics, and immunization is recommended for children under six years of age, while for those from six to ten years, and adults less than 35 years of age, immunization is recommended if the Schick test is positive. Persons traveling to regions where yellow fever and typhus fever are endemic should be given the corresponding vaccine. Since cholera vaccination usually becomes ineffective after six months to one year, this vaccine as well as that for plague usually can be given by local health services when cases are prevalent or when an epidemic is encountered. Yellow fever immunization is required for most of South and Central America; Africa; and Asia, when the traveler has passed through Africa. Also, Ceylon, India, and Pakistan prohibit entry unless yellow fever vaccine has been given before 12 days of arrival.

Routine immunizations against smallpox, typhoid and paratyphoid fevers, diphtheria and tetanus, as well as the vaccine for epidemic typhus fever can be given by the traveler's personal physician. Other vaccines, such as that for yellow fever, may not be easily available to the family physician and they may be received at a United States Public Health Service Clinic or Quarantine Station.

Schedules of immunization, including initial and stimulating or "booster" doses for smallpox, typhoid and paratyphoid fevers, tetanus and diphtheria, and for yellow fever, epidemic typhus, cholera, and plague are given in table I.

Dosages of immunization for smallpox, typhoid and paratyphoid fevers, tetanus and diphtheria, and for yellow fever, epidemic typhus, cholera, and plague are given in table II.

RECOMMENDED PERSONAL PRECAUTIONS

Disease-producing organisms in water and food are the principal causes of the simple diarrheas, food poisonings (staphylococcal toxin, and salmonella), bacillary dysentery (shigellosis), typhoid and paratyphoid fevers, amebic dysentery or intestinal amebiasis (*Endamoeba histolytica*), cholera (*Vibrio cholerae*), as well as other parasitic infections, such as roundworm (ascariasis), whipworm (trichuriasis), trichinosis, and tapeworm (teniasis).

Foods, particularly meat, milk and fish, spoil rapidly in tropical climates unless they are kept refrigerated. Cooked foods that are kept at ambient temperatures are excellent culture media for the growth of bacteria. It is evident that only slight initial bacterial contamination is necessary, since the rapid growth of bacteria can produce highly dangerous contamination within only a few hours. The usual sources of such bacterial contamination are infective respiratory (staphylococcal) and intestinal discharges, and skin infections (staphylococcal) of food handlers who are insanitary in their habits and personal hygiene.

Meat from infected animals often contains parasites and unless thoroughly cooked

can serve to transmit them to man. Fresh milk, or butter and ice cream made from it, can be highly infective.

Root and leafy vegetables may be contaminated in fields that are fertilized with human excreta, or may be contaminated by freshening in drainage water or even sewage to improve marketability.

Houseflies and cockroaches also can carry disease producing organisms from human excreta and other wastes to foods that are kept exposed in the kitchen or in the dining room.

Since the traveler, while in the hotel or restaurant, can seldom observe the preparation, storage, and handling of food and water that may be served to him, he can effectively avoid these infections by not consuming: water that is not freshly boiled, ice, sherbets and ices; meat that is not thoroughly cooked; milk that is not boiled,

TABLE I

Preventive Inoculations Required and/or Recommended for Foreign Travel

Inoculum	Immunizing Doses			Booster Doses	
	Number	Intervals	Begin Prior to Departure	Required	Recommended
Smallpox vaccine	1	—	Required within 1 year prior to departure		Every 3 years; and if exposed to disease
Typhoid-paratyphoid vaccine	3	7–10 days	21 days		Annually; and if exposed to disease
Diphtheria toxoid (Alum precip. or aluminum phosphate adsorbed)	3	28 days	60 days		If Schick test becomes positive
Tetanus toxoid (Alum precip. of aluminum phosphate adsorbed)	2	28 days	30 days		One year after initial series; wounds or burns
Typhus vaccine (Epidemic Cox-type)	2–3	5–7 days	21 days		Annually where disease is prevalent; or if exposed
Yellow fever vaccine†	1	—	Required before 12 days of arrival—Ceylon; India; Pakistan		Every 4–6 years while in endemic areas
Cholera vaccine	2	7 days	*		Intervals 3–6 months if disease is prevalent; or if exposed
Plague vaccine	2	7 days	*		Intervals 3–6 months if disease is prevalent; or if exposed

* May be administered by local health services when cases are prevalent or epidemic is encountered.

† Smallpox and yellow fever vaccines should be given at least 5 days apart.

TABLE II

Regimens of Immunization

Inoculum	Immunizing Doses				
	Number	Intervals	Adults	Children	Administration
Smallpox vaccine	1	—	1 drop	1 drop	Epidermal—Multiple Pressure—10 for 1° Immunization—30 for Revaccination
Typhoid-paratyphoid vaccine	3	7–10 days	Each 0.5 ml.	If over 6 mos.; based on wgt.	Subcutaneous—initial series; 0.1 ml., intradermal for booster
Diphtheria toxoid (Alum precip. or aluminum phosphate adsorbed)	3	28 days	Each 0.5 ml.	Each 0.5 ml.	Intramuscular
Tetanus toxoid (Alum precip. or aluminum phosphate adsorbed)	2	28 days	Each 0.5 ml.	Each 0.5 ml.	Intramuscular
Typhus vaccine (Epidemic Cox-type)	2–3	5–7 days	Each 1.0 ml.	If over 6 mos.; based on wgt.	Subcutaneous Intramuscular
Yellow fever vaccine	1	—	0.5 ml.	0.5 ml.	Intramuscular
Cholera vaccine	2	7 days	0.5 ml. 1.0 ml.	If over 6 mos.; based on wgt.	Subcutaneous
Plague vaccine	2	7 days	0.5 ml. 1.0 ml.	If over 6 mos.; based on wgt.	Subcutaneous

locally produced butter, soft cheeses, and ice cream; vegetables that are not cooked, including those used in salads and garnishes; raw fruits with thin skins; melons; custards, puddings, cold pastries, and meringues.

Two aphorisms that should be applied to foods in the tropics are: "Eat no fruit or vegetable raw that does not have an unbroken skin, and which has not been well washed and peeled or skinned by oneself immediately prior to eating. Boil or bake all others." "Keep the pease porridge hot or keep it very cold, but beware of porridge in the pot nine days old; or even a few days or even a few hours."

Even if the food handler may not have washed his hands, the traveler in the tropics should not perpetuate the offense by neglecting to wash his own hands before eating.

The anopheline mosquitoes, the vectors of malaria, are by far the most medically important insects of the tropics. Other species of mosquitoes may transmit yellow fever, filariasis, and dengue in regions where these diseases are endemic. Houseflies and cockroaches are prevalent throughout most of the tropical world and are important insofar as they serve to spread intestinal infection. Other arthropods, such as sandflies, lice, ticks, mites, tsetse flies, and reduviid bugs, are responsible for transmitting serious infectious diseases in diverse parts of the tropics. Many of the

latter group infest native dwellings in the poorer quarters of cities and also in rural areas. In those parts of the tropics where typhus fever, relapsing fever, Chagas disease, or plague are endemic, the traveler definitely should not visit insanitary native houses.

Since anopheline mosquitoes usually are night feeders, it is important to sleep under mosquito nets or in screened rooms while in malarious areas. Also, it should be the rule when in these areas to remain indoors in screened buildings after nightfall, especially where insecticiding programs either have not been inaugurated or have been poorly maintained. Thus, such seemingly harmless amusements as after dark visits to native houses and ceremonies, beach parties, and outdoor movies are precluded.

When trips are made into malarious rural areas, even when such other precautions, as covering clothing, bednets, and insect repellents are used, suppressive medication with chloroquine (Aralen) is advisable at least during the period of exposure.

Unfortunately it is not possible for the traveler to control flies and to keep them from contaminating his food. If the traveler observes that the hotel or restaurant at which he is living or eating is fly ridden, it is very possible that the place is insanitary with fly breeding places near by, and he would be wise to move to a better run establishment.

Travel-aid kits (most of the contents* of which the writer has been recommending for travelers to the tropics during the past several years) should be assembled for purchase by prospective travelers and supplied on prescription by the physician for essentially emergent use in symptomatic, prophylactic, and anti-infective treatment. It should contain instructions for using these medications, preferably under supervision of a local physician when available, as well as some of the aforementioned information. Obviously, some recommendations will differ according to the itinerary.

Inasmuch as infections acquired during visits to certain foreign countries may have long periods of latency and may become manifest only after some months or even years, the carriers cannot be content merely to provide a safe and pleasant cruise but must be concerned with the health of the traveler until he returns home. Although the enticing beauty of tropical spots, their hotels with price ranges and accommodations are elaborately described in colorful folders, almost nothing is done to assure the traveler that he will not become infected through no fault of his own. It also would seem important that frequent unannounced inspections of the hotels' food and water supplies, food handlers, and sanitary facilities not only for the guests but for the food handlers as well, be made jointly with local government health authorities before they are approved for tourists. It is improbable that local governments would seriously object to such inspections, since it would be to their financial advantage to have healthy satisfied visitors who later would recommend their country as a place to visit and spend a carefree and healthy vacation.

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* Symptomatic—Aspirin, Chlor-Trimeton tablets, Thorazine or Apolamine, paregoric, Chlor-Trimeton Cream 1%, Creamalin tablets. Prophylactic—Bonamine, Bio-Band Adhesive strips, Aralen, Diodoquin tablets, Desenex powder, and occasionally iodine water-purification tablets. Therapeutic anti-infective—Terramycin crystalline tablets, 250 mg., or Terramycin SF, 250 mg.

GENERAL PRACTICE CLINICS

This monthly section of General Practice Clinics features reports of papers delivered at current medical meetings in the United States and abroad.

The New Steroids and Things to Come

Presented by JOSEPH J. BUNIM, M.D. (National Institute of Arthritis and Metabolic Diseases and Johns Hopkins University) before the County Medical Society, Philadelphia, Pa., May 11, 1955.

The work of Reichstein with aldosterone, which has no antirheumatic properties, and of Fried, who in 1954 developed a halogenated steroid with greatly increased electrolytic effects and improved antirheumatic effects, were discussed. The halogenated steroid, 9-alpha-fluorohydrocortisone, causes so much salt and water retention that it is not practical for rheumatoid arthritis. A few months after Fried made his contribution, research scientists of Schering developed a new synthetic compound, which is nontoxic and causes a fall in eosinophila, involution of the thymus, deposition of glycogen in the livers of adrenalectomized rats without causing sodium retention, as demonstrated in animal experiments. The names given these two synthetic compounds were prednisone and prednisolone.

The compounds differ from cortisone and hydrocortisone respectively in having a double bond between carbons 1 and 2. Patients who have stopped responding to the original steroids will respond to the new synthetic compounds.

A series of 15 patients who had had rheumatoid arthritis for from 2 to 25 years was presented. Only 3 patients had never received cortisone, hydrocortisone, or ACTH. Gold, phenylbutazone, and salicylates had also been used in some. Improvement on prednisolone was dramatic, sometimes being evident within a few hours. The erythrocyte sedimentation rate fell promptly but rose again slightly on maintenance therapy (20 to 30 mg. per day); hematocrit rose; serum cholesterol also rose, but the esters did not. Maximum objective effects were often not seen until three or four weeks after therapy was started.

Results obtained included: remissions during therapy, 8; major improvement, 5; minor improvement, 2; no improvement, 0. Suppression of adrenocortical function was observed. In most of these cases, the sedimentation rates returned to normal. Urine and stool studies showed no sodium or potassium retention or negative nitrogen balance when therapeutic doses were given. Histologic examination of joint tissues showed that characteristic rheumatoid arthritis changes are largely reversed in 24 days of prednisolone therapy. Side effects observed were: epigastric discomfort (transitory), sleeplessness and restlessness, increased sweating and flushing, facial rounding, and hirsutism. Weakness and fatigue, mental changes (one frank depressive psychosis developed), duodenal ulcer, and acneiform eruption were also observed. None of the patients showed a glycosuria, but some did show elevated levels on glucose tolerance tests while on treatment.

These new compounds are four times more potent than cortisone and hydrocortisone without a corresponding increase in side effects, but they are not free from side effects. They have all the limitations that the other steroids have and should never constitute the only therapy. Careful selection of patients is called for.

The Clinical Use of Erythromycin

Presented by SAUL SOLOMON, M.D., before the Clinical Society of the Polyclinic Hospital Meeting, New York City, May 2, 1955.

This study consisted of one year of clinical and bacteriologic experience with erythromycin at Bellevue Hospital. There were 122 patients including: 88 cases of pneumonia, primarily due to grampositive organisms; 20 cases of nonspecific respiratory infections; and 14 miscellaneous infections, including erysipelas, furunculosis, staphylococcal otitis, a staphylococcal subdiaphragmatic abscess, and a human bite with infection that subsided within 48 hours on erythromycin therapy. In this group there were also a successfully treated case of chronic osteomyelitis, a drug addict with tetanus (who received specific therapy), and a staphylococcal sepsis and meningitis that did not respond to penicillin and streptomycin but cleared on erythromycin.

Dosage used in these patients, all of whom were adults, was 400 mg. orally every four hours. Side reactions were few, consisting of a few cases of mild diarrhea, rash, and nausea, and vomiting. In only 1 case did side reactions necessitate stopping therapy.

In this series, sensitivity studies revealed that the staphylococci were uniformly sensitive to erythromycin; they were resistant in close to 50 per cent or more of the cases to penicillin, and on 27 to 80 per cent to the other antibiotics tested. Only one case of erythromycin resistance was encountered. Erythromycin was also noted to be active against *Hemophilus influenzae*. Other gramnegative organisms such as *Escherichia coli*, *Pseudomonas*, and *Proteus* were resistant to erythromycin. Erythromycin was found to be an effective antibiotic against gram-positive organisms. It was especially useful with the emergence of resistant staphylococci, where erythromycin seemed to be the drug of choice in acute cases. Its other advantages included its lack of a broad spectrum, thus reducing complications associated with fungal overgrowth, and its relatively low toxicity at therapeutic doses.

Antibiotics in Childhood

Presented by HARRY SHWACHMAN, M.D., before the Massachusetts Medical Society, Boston, Mass., May 18, 1955.

With the relatively widespread use of antibiotics in the home, a number of sick children who failed to respond are referred to the hospital for diagnosis and treatment. In some of these patients the diagnosis of purulent meningitis is made without bacteriologic confirmation. Measures to obtain specific diagnosis followed by specific chemotherapy is urged. A number of cases are shown in which a rise in

meningococcal antibody titre of the serum was the only evidence that the patient had had a meningococcal infection. Over the years *H. influenzae meningitis* has replaced tuberculous meningitis as the most predominant type encountered in childhood. Next in order is meningococcal followed by pneumococcal and a variety of other organisms with relative infrequency.

The therapy of purulent meningitis is far from standardized. A number of questions are still unsettled, such as intrathecal use of antibiotics, the choice of the agent, and/or the combination of agents. In spite of these problems the mortality has been reduced to between 5 per cent and 10 per cent in many pediatric centers. Several workers treat all purulent meningitis with a combination of chloramphenicol and sulfadiazine; others are using oxytetracycline and sulfadiazine. In meningococcal meningitis sulfadiazine remains the drug of choice, but penicillin is frequently added. Although some strains of meningococci are resistant to sulfadiazine in the test tube, no in vivo failure with sulfadiazine has been encountered. In treating pneumococcal meningitis, penicillin is the best single agent. Massive doses given intravenously every three hours are recommended. When sulfadiazine is employed the blood levels should be in the neighborhood of 10 to 15 mg. per cent. Brief mention was made of the complication of subdural collection of fluid in all forms of purulent meningitis.

The liberal use of antibiotics has made it difficult to recognize other deep-seated infections such as osteomyelitis. In a recent study at Yale it was impossible to make a bacteriologic diagnosis in 13 of 99 successive cases of this disease. The detailed case history of a boy with a latent staphylococcal osteomyelitis was discussed.

A few examples in the treatment of gram-negative infections were shown, a case history of a child with typhoid fever, which was diagnosed 24 hours after admission, was also presented. The rarity of this infection is indicated by the incidence of about one case per year in the author's hospital. This particular patient had been given several antibiotics on the outside. He responded favorably when chloramphenicol was instituted. The use of cortisone during the toxic phase was mentioned. The difficulty of eradicating the organism is demonstrated in this particular case by showing that the typhoid bacillus was recovered from the stool two days after chloramphenicol was discontinued. Also mentioned was the recent work from England in which a new technique of blood cultures demonstrates that typhoid bacilli may be recovered from the blood stream in fairly large numbers, whereas the routine techniques reveal no organisms.

A discussion of the prophylactic use of penicillin in rheumatic fever was presented. Penicillin rather than sulfadiazine was recommended for the therapy of beta-hemolytic streptococcal infections. Prophylactic penicillin therapy is also recommended for patients with cardiac lesions who undergo dental surgery or oral manipulations. Some workers believe in the routine prophylactic use of antibiotics in the premature. The author feels it is better to reserve their use until infections are encountered for which a specific agent is selected. Case illustrations of resistant infections as well as superinfections were presented. The rare condition known as agammaglobulinemia, either acquired or congenital, should be kept in mind when

dealing with patients having recurrent infection. A number of children with mucoviscidosis have been treated continuously with chlortetracycline and oxytetracycline for as long as four and five years. None of the serious complications such as colitis and monoliasis have been encountered. A new complication is noted, namely a dark brown or black discoloration of the teeth in some children who have been given chlortetracycline for four or five years.

Needle Biopsy of the Kidney

Presented by MAXWELL WESTERMAN, M.D., before the Blockley Research Society, Philadelphia, Pa., May 19, 1955.

This procedure is used chiefly in diagnosis but is a valuable adjunct in the study of renal disease. The patient must first be evaluated for hemorrhagic tendency, by prothrombin time, bleeding time, and platelet count. Roentgenograms are then taken for abnormalities in anatomy and position; an anterior kidney-ureter-bladder film being satisfactory. Palpation is also performed, usually on the right kidney. With the patient in a sitting position, the approach is made utilizing the roentgenograms, approximately one inch below the costal margin and one inch lateral to the back muscles. The area is first infiltrated with procaine. Movement of the needle with respiration is evidence that the needle is in the kidney; either a Francine or Vim-Silverman needle is used.

The procedure has been used to diagnose disseminated lupus, Kimmelstiel-Wilson disease, and amyloidosis as well as to determine the correlation between renal anatomy and function. The biopsy may also be used prognostically. The best therapeutic response in nephrosis is reported in cases where minimal renal changes are present. This can be determined by biopsy.

The Nephrotic Syndrome in Children

Presented by DONALD GRIBETZ, M.D., (Pediatric Department of Mt. Sinai) before the Clinical Conference on the Nephrotic Syndrome at Mt. Sinai Hospital, February, 1955.

There have been many recommended forms and schedules of therapy for nephrosis in children. The one that at present seems to offer the most promise is treatment with the newer pituitary and adrenal hormones. These substances have been utilized for two purposes: production of an immediate diuresis and prolonged maintenance therapy. In the combined series at the Boston Children's Hospital and New York Babies Hospital, diuresis was produced in 70 per cent of more than 200 trials with either ACTH or cortisone. Because of the ability to cause diuresis and to produce apparent reversion of the chemical abnormalities associated with this disease, ACTH and cortisone are now being tried as maintenance therapy in children with nephrosis at many centers including Mt. Sinai Hospital.

It is postulated that these agents may exert their beneficial effects by decreasing glomerular permeability, increasing glomerular filtration rate, or by decreasing a

theoretical antigen-antibody reaction. Whatever the mechanism, it is hoped that prolonged maintenance therapy may alter the basic pathology of this disease, decreasing morbidity and mortality.

The present regimen at Mt. Sinai includes the use of cortisone in a dosage of 400 mg. per sq. meter per day, or ACTH at a rate of 150 to 200 mg. per sq. meter for 10 to 14 days with abrupt stoppage for diuretic purposes. Once diuresis is achieved, cortisone is administered for three consecutive days out of each week at the above dose level. This maintenance therapy is presently being continued indefinitely.

The Value of an Optimal Effective Dose of Anticholinergic Drugs in the Treatment of Peptic Ulcer

Presented by DAVID C. H. SUN, M.D., AND HARRY SHAY, M.D., (Temple University School of Medicine) before the American Medical Association, Atlantic City, June 8, 1955.

The optimal effective dose (OED) is the maximal dose which produced dryness of the mouth but no other uncomfortable symptoms of parasympathetic inhibition. It is determined by starting the manufacturer's recommended dose three times a day before meals and at bedtime on the first day, increasing by one increment daily until uncomfortable symptoms of parasympathetic inhibition occur, then decreasing by one increment daily until symptoms disappear. The increments of the drugs studied were: Elorine sulfate, 50 mg.; mepiperphenidol (Darstine) bromide, 50 mg.; propantheline (Probanthine) bromide, 15 mg.; tincture of belladonna, 2 drops.

Using the criterion of suppression of gastric acidity to the level of *p*H 4.5 or higher, Elorine sulfate was effective in all of 16 patients, the effect lasting longer than three hours in 9 of them. The OED varied from 150 to 500 mg. (1.5 to 9.01 mg./Kg.) in individual patients. Darstine was effective in all of 13 patients, with an OED of 50 to 400 mg. (1.04 to 5.45 mg./Kg.). Probanthine was effective in 11 of 12 patients, with an OED of 30 to 120 mg. (0.53 to 2.18 mg./Kg.). Belladonna was effective in only 2 of 5 patients, the OED being 22 to 35 drops. Thus in order to administer an effective dose of an active anticholinergic drug, one needs to tailor the dose of the drug to each patient and not administer it according to body weight or any recommended uniform dose.

The authors reported results showing uniform inhibition of basal gastric secretion to *p*H 4.5 or higher by a single optimal effective dose of an active anticholinergic drug, and its superiority over a single "recommended" dose in inhibiting "digestive" secretion and secretion induced by emotional stress and insulin hypoglycemia. They thus advocated the use of the optimal effective dose of these drugs in the clinical management of peptic ulcer disease, if elimination of peptic activity is considered essential for complete healing of the ulcer. The absence of any untoward side effects on prolonged administration of these drugs makes this dosage schedule practical for clinical use.

The Effect of Antibiotics on Intestinal Absorption of Vitamin B_{12} in Disorders of the Gastrointestinal Tract

Presented by JAMES A. HALSTED, MARIAN E. SWENDSELD, MARVIN GASSTER, AND PETER M. LEWIS before the Western Society for Clinical Research, Carmel, Calif., January 28–29, 1955.

These studies were prompted by reports that various antibiotics produced a reticulosis in patients with pernicious anemia and other megaloblastic anemias. With the use of radioactive (Cobalt-60 labeled) Vitamin B_{12} given orally and determining the amount excreted in the stools, the authors studied the effect of various agents on the absorption of Vitamin B_{12}.

Administration of intrinsic factor to patients with pernicious anemia or total gastrectomy significantly increased the absorption of vitamin B_{12} while there was no effect seen in normal subjects or those with small intestinal disease.

It was found that chlortetracycline or tetracycline given in a dosage of 2 Gm. per day had no effect on the absorption of vitamin B_{12} in patients with pernicious anemia, total gastrectomy, nontropical sprue, or regional enteritis. There was, however, a markedly increased absorption of vitamin B_{12} produced by these antibiotics in 3 patients with the "blind loop syndrome."

The authors theorize that in the case of intestinal stasis associated with a blind loop, the decreased absorption of vitamin B_{12} may be due to absorption of the vitamin by bacteria which decreases the amount available for absorption by the patient. It is possible that the antibiotics, by decreasing the bacterial population, decrease this competitive use of vitamin B_{12} by the bacteria, allowing more to be absorbed by the host.

Iatrogenic Aspects of Cardiovascular Disease

Presented by PERRIN H. LONG, M.D., (College of Medicine, State University of New York) before the New York Heart Assembly, Rochester, New York, March 17–19, 1955.

Physicians themselves can produce heart disease, sometimes by the drugs they use in therapy, and sometimes by the words they use to their patients; in the case of drugs, serum sickness may produce cardiac arrhythmias. Since most patients recover from the disease, there are few opportunities to study the pathologic lesions of this type of hypersensitivity. But several reports exist of atrial and myocardial damage associated with serum sickness or with intoxication from sulfonamides.

The most common instance of a iatrogenic heart disease is that due to digitalis therapy. Frequently, because the clinical end point for digitalis therapy is difficult to determine, the physician continues to administer digitalis therapy until toxic signs appear. Then he attempts to establish a maintenance dose which just falls short of toxicity.

The incidence and severity of digitalis poisoning are continuing to increase. This is the result of using concomitantly with it diuretics such as mercurials, Diamox (carbon anhydrase inhibitor), ammonium chloride, cortisone, ACTH,

parenteral fluids containing electrolytes, and ion exchange resins. All these affect the electrolyte balance, and shifts in electrolytes in patients with congestive heart failure frequently change the reaction of the myocardium to digitalis.

The most important electrolyte is potassium, but too little thought is given it by the physician. Even without digitalis, hypokalemia and hyperkalemia may have a deleterious effect on the heart and bring about definite changes in the ECG. When digitalis is given in toxic doses, potassium is liberated from both heart and striated muscle. There is evidence that under certain circumstances the administration of potassium, by decreasing the response of heart muscle to digitalis, lowers or abolishes the toxic manifestations of digitalis.

Fortified Broad-Spectrum Antibiotics as an Adjunct in Surgical Treatment of the Young and the Aged and Debilitated Patient

Presented by AARON PRIGOT, M.D., (Harlem Hospital) before the Conference on Nutrition in Infections, New York Academy of Sciences, New York City, May 24–25, 1955.

The introduction of the broad-spectrum antibiotics in the treatment of surgical infections placed in the hands of the surgeon potent anti-infection agents. Because the duration of the acute phase of such illnesses has been considerably reduced through antibiotic therapy, a certain laxity in the total care of the patient has resulted. It is to be remembered that once the acute phase of an infection is over, the reparative process is still in operation and is, in large measure, dependent on the nutrition of the patient and on nutritional therapy. This latter factor is of even greater importance in the young, in the aged, and in the debilitated patient. The disease process itself causes a reduction in the available nutrient factors through decreased absorption, decreased utilization, and increased demand. The wide range antibiotics may also have an effect on this equilibrium through side reactions and through the alteration of the intestinal flora.

For this study the author selected 25 cases of severe surgical infections in patients with severe fractures and two patients with extensive burns, one a child and the other an adult. The antibiotics employed were oxytetracycline and tetracycline, available both in tablet form and in a suspension for pediatric use. Each dose contained 250 mg. of the antibiotic, fortified with the following vitamins: ascorbic acid 75 mg.; thiamine hydrochloride 2.5 mg.; riboflavin 2.5 mg.; niacinamide 25 mg.; pyridoxine hydrochloride 0.5 mg.; calcium pathothenate 5. mg.; vitamin B_{12} 1 μg.; folic acid 0.375 mg.; and menadione (vitamin K analogue) 0.5 mg. Adults received four doses daily and children proportionately less.

The combination was well tolerated by all patients. In no case were any side reactions observed nor was withdrawal of medication necessitated by allergic or toxic manifestations. All the patients made an eminently satisfactory recovery. The ease of administration of the antibiotic and the nutritional supplement at the same time reduced the number of pills taken by the patient, decreased the number of medications to be administered by the nursing service, and decreased the incidence of failure by the patient to take the prescribed medication.

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*Cass, L. J., and Frederik, W. S.: Ann. New York Acad. Sc. 58:455 (July 15) 1954.

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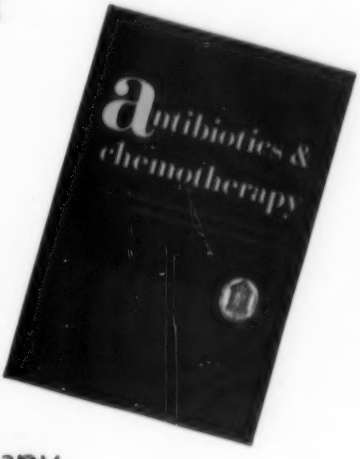

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